DEVELOPMENT OF NOVEL PHOTOCATALYTIC AND NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS FOR THE FACILE ACCESS OF FUNCTIONALIZED MULTIFLUORINATED ARENES

By

SAMEERA M. SENAWEERA

Bachelor of Science in Chemistry
University of Kelaniya
Sri Lanka
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Dissertation Approved:

Dr. Jimmie D. Weaver

Dissertation Adviser

Dr. Richard A. Bunce

Dr. Ronald J. Rahaim

Dr. Christopher Fennell

Dr. Jennifer H. Shaw

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Abstract: Functionalized multifluorinated arenes are an important class of molecules, because the incorporation of fluorine can alter or enhance the properties of a molecule. Since there have been no naturally occurring fluoroaromatics identified, all the aryl fluorides must be synthesized. While the selective installation of fluorines to synthesize multifluoroarenes is challenging, perfluoroarenes and heteroarenes can be produced industrially on scale, and represent an ideal starting point for the synthesis of multifluorinated arenes. However, due to the short and strong nature of the C–F bond, subsequent functionalization is challenging. As a part of the C–F functionalization program in the Weaver lab, the work presented in this dissertation is focused on development novel methodologies to access functionalized, partially fluorinated aromatics. In this approach, the goal is to selectively remove or functionalize the undesired fluorines of perfluoroarenes while keeping the desired fluorines intact. In this vein, we have shown that a key perfluoroaryl radical intermediate can be formed *via* photocatalytic electron transfer and can be selectively functionalized. The possibility for this radical to undergo facile reduction and arylation is discussed. The development of these methods has rapidly expanded the synthetic possibilities of multifluorinated arenes and has outpaced the availability of more complex polyfluoroaryl starting materials. In order to circumvent low availability of functionalized fluoroaryl building blocks, nucleophilic aromatic substitutions (S_NAr) with fluoroarenes have also been explored. One example is the addition of Meldrum's acid to polyfluoroarenes which generates a novel class of compounds that can serve as a synthon for α-perfluoroaryl acetic acids. Some nucleophilic additions require extreme conditions which severely limits their utility. To overcome the inherent difficulties associated with chlorodefluorination, a catalyst was developed in which an aromatic donor-acceptor interaction was identified as a key feature. This catalyst facilitated the development of a mild method for the chlorodefluorination of perfluoroarenes. The synergistic use of photocatalysis and S_NAr chemistry is an expedient way to access functionalized polyfluoroaromatics and is also discussed in this dissertation.

TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

Table Page

Table Page

LIST OF FIGURES

Figure Page

LIST OF SCHEMES

Scheme Page

Scheme Page

Scheme Page

CHAPTER I

PHOTOCATALYTIC C–F REDUCTION AND FUNCTIONALIZATION

1.1 Importance of fluoroaromatics and effect of fluorination

Fluoroorganic molecules have become an extremely important and valued class of molecules in a variety of fields, namely, pharmaceuticals,[1] agrochemicals[2] and industrial applications. Among the diverse industrial applications where organofluorines are prevalent, such molecules are used as functional materials such as liquid crystals,[3] organic light-emitting diodes (OLEDs),[4] water-splitting sensitizers,[5] and electron transport materials (Figure 1.1).[6] It is now more than 70 years since the first fluorinated natural product, fluoroacetate, was identified in 1943.[7] During the intervening time only about a dozen more fluorinated natural products have been isolated and characterized.[8] Even though most of the above mentioned modern applications rely on the use of fluoroaromatics, no naturally occurring aryl fluorides have yet to be identified. After the invention in the 1950s of the first fluorine containing pharmaceutical, fludrocortisone,[1a] the field started growing rapidly. By 2013, 20–25% of drugs in the pharmaceutical pipeline contained at least one fluorine atom.[1a, 1b] Furthermore, a survey of commercially approved herbicides which

was carried out in 2014 revealed that almost 25% of them (56 compounds from 229) contain at least one fluorine atom in their structure.[9]

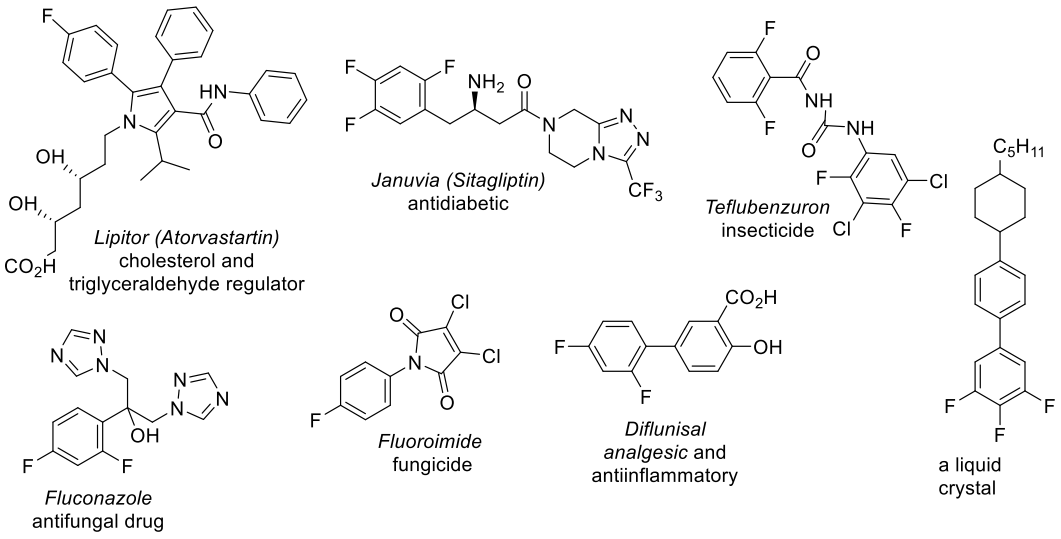
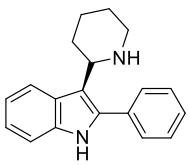
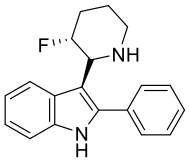
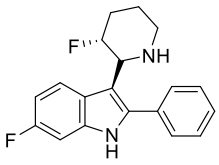


Figure 1.1 Pharmaceutically and industrially important fluoroaromatics

Incorporation of fluorine into the structure of a drug can modulate molecular properties. Modulation of p*K*a often impacts the bioavailability of a molecule, which is the percentage of the dose reaching the circulatory system and is denoted by F%.[1b] In contrast to intravenous drugs which are considered 100% bioavailable, the bioavailability of drugs which are orally administered often decreases due to either poor absorption through the gut membrane or enzymatic degradation. Fluorine, as the most electronegative element ($\chi_{(pauling)}$ 4.0 for F *vs.* 2.2 for H)[10] has a significant electron withdrawing ability and can affect the basicity of nearby amine groups. For instance, fluorinated analogs of 3-piperidinylindole antipsychotic drugs (Table 1.1) show a significant basicity change of the amine and consequently a greater bioavailability.[1b] The stomach is acidic pH (pH =1 -3), and amines form the corresponding ammonium salts of the compounds. Since the membrane does not allow ionic compounds to pass, these ammonium compounds cannot be absorbed at the right time. Fluorine incorporation decreases the formation

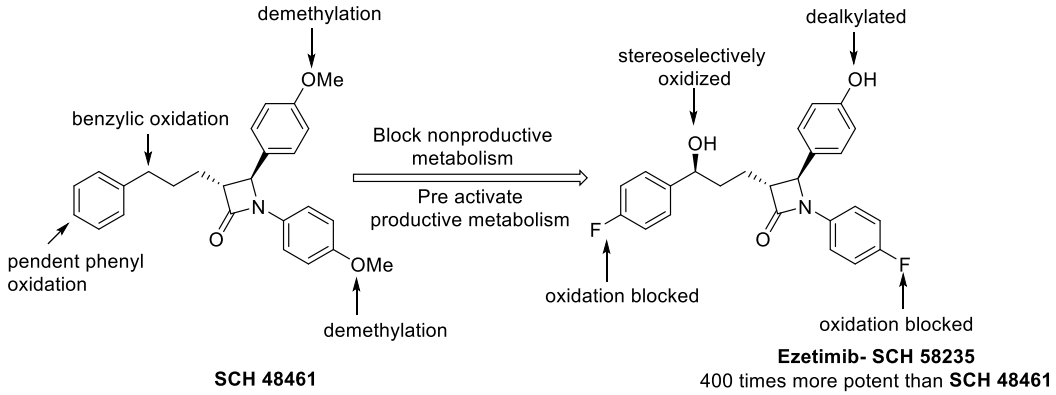
of ammonium salts by decreasing of the basicity of the N *via* inductive effects and thereby increases the bioavailability.

Table 1.1 p*K*a and bioavailability altered by fluorination

	Indole		
			
*p*Ka of the corresponding ammonium salt	10.4	8.5	-
Bioavailability (F%)	Poor	18	80

Lipophilicity is also a crucial factor for a drug molecule to pass through a biological membrane. Inclusion of fluorine can be used as a handle to modulate lipophilicity of the molecule of interest. While monofluorination and trifluoromethylation of saturated alkyl compounds usually decrease the lipophilicity due to the strong electron withdrawing capabilities of the fluorine, per/polyfluorination of aromatics and fluorination adjacent to atoms with π-bonds usually increases lipophilicity.[1b] Alkyl C–F bonds are highly polarized due to the electronegativity difference (i.e., the carbon atom has a partially positive charge and the fluorine is partially negative). When C–F bonds are attached to π systems, electrons in p-orbitals of fluorines encounter a totally different situation. The p-orbital at fluorine stays parallel to the p-orbital of carbons which are in conjugation. Therefore, both the size and the geometry fit perfectly to get an optimum overlap. The dipole resulting from the σ-electronegativity will force a partial replacement of electric charge from fluorine towards carbon and the aromatic ring (i.e., fluorine behaves as a σ-electronegative, but as a π-electropositive element) thus, aromatic C–Fs become relatively non polarizable and lipophilic when compared to alkyl C–Fs.[1b] Another property which is altered upon fluorination, and is vital within pharmaceuticals, is metabolic stability. Poor metabolic stability caused by oxidative processes mediated by cytochrome P450 is a common problem in drug development. Sometimes oxidative degradation simply leads to

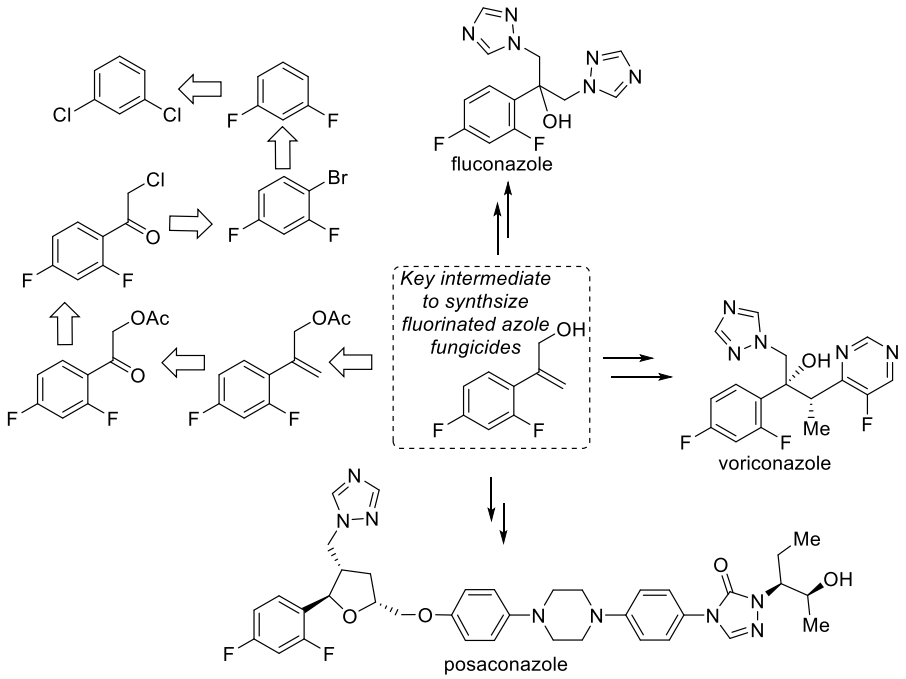
inactive compound, but in some cases, it can result in toxic metabolites. Thus, controlling the metabolic fate of drug molecules is an important objective. In some cases, this problem can be circumvented by blocking metabolically labile sites with fluorine substituents. This is exemplified in the lead optimization Ezetimib, a cholesterol inhibitor. The potency of the drug was increased by reducing the undesired metabolism of the drug, which allowed it to keep a satisfactory circulation concentration. During the development of the drug, productive sites which are labile to P450 were derivatized (i.e., the benzylic position was intentionally oxidized and the OMe group was intentionally demethylated) to increase the potency while, the nonproductive sites were blocked by fluorines to minimize the oxidation by cytochrome P450 as shown in Scheme 1.1.[1b]



Scheme 1.1 Enhanced potency as a result of improved metabolic stability upon fluorination

Close inspection of the fluoroaromatics used in pharmaceutical and industrial applications, reveal some common structural features. Most 1) are not perfluorinated, 2) are densely functionalized to perform a desired role/s, and 3) serve as a terminating group. It seems the last observation is likely, at least in part, due to the unavailability of complex multifluorinated precursors as well as the lack of satisfactory methods to further functionalize existing fluoroaromatic starting materials. Stated differently, within pharmaceuticals, aryl fluorides are typically attached to the remaining molecule by a single point, i.e. the aryl fluoride is not found

internally (the fused fluoro-antibiotics being the exception). Typically, the synthesis of such molecules starts with the desired fluorines already present on the parent molecule with the correct regiochemistry. Take for instance the fluorinated azole fungicides as depicted in Scheme 1.2, which share a common difluorinated intermediate that is derivatized to synthesize different commercially available fungicides. Specifically, notice 1) how all the molecules attach to the fluoroarenes in one position, and 2) in all cases it serves as the terminating group. Despite the simple nature of the intermediate molecule, the shortest synthetic sequence to access that require at least six steps starting from 1,3-dichlorobenzene. The unfortunate consequence is that structural activity relationship studies regarding organofluorines are woefully incomplete.

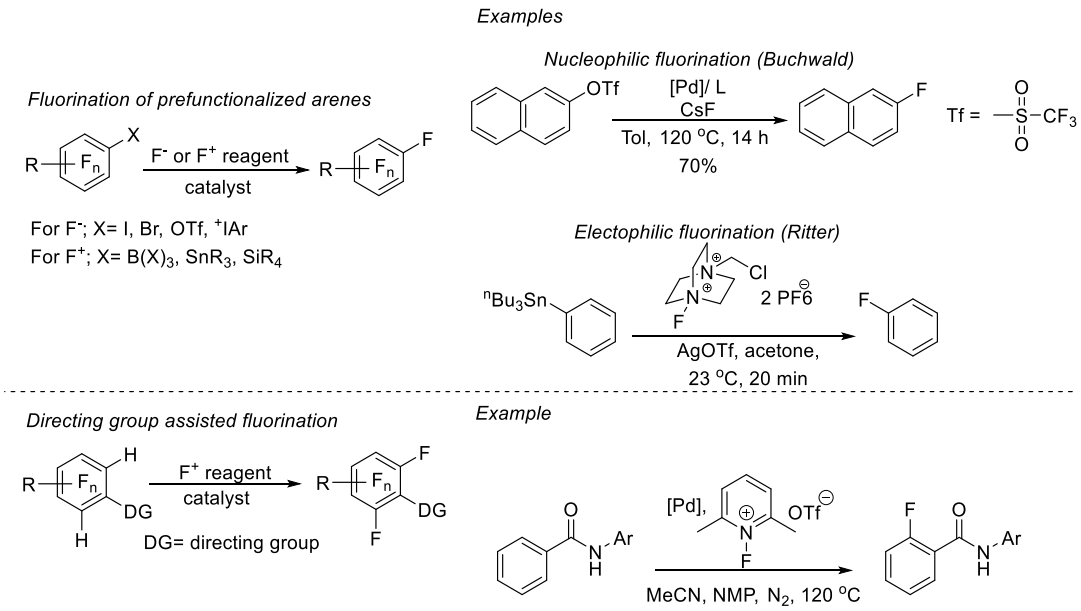


Scheme 1.2 Current lengthy synthesis of the common intermediate for azole fungicides

1.2 Selective fluorination

Recently, more efforts have been devoted to fulfill the need of fluoroaromatics *via* selective fluorination.[11] Such methods include both electrophilic[12] and nucleophilic[13]

fluorinations as well as C–H fluorinations assisted by directing groups[14] (Figure 1.2). However, all of these methods need prefunctionalization of commercially available molecules prior to the substitution step. Furthermore, to accomplish directed fluorination requires both the installation and the removal of a directing group (i.e., amide group) which adds more steps to the synthetic procedure. More importantly, these groups can only direct the substitution *ortho*- to itself. This phenomenon drastically limits the use of this method to access complex multifluorinated arenes due to its inability to allow *meta*- or *para*- fluorination.



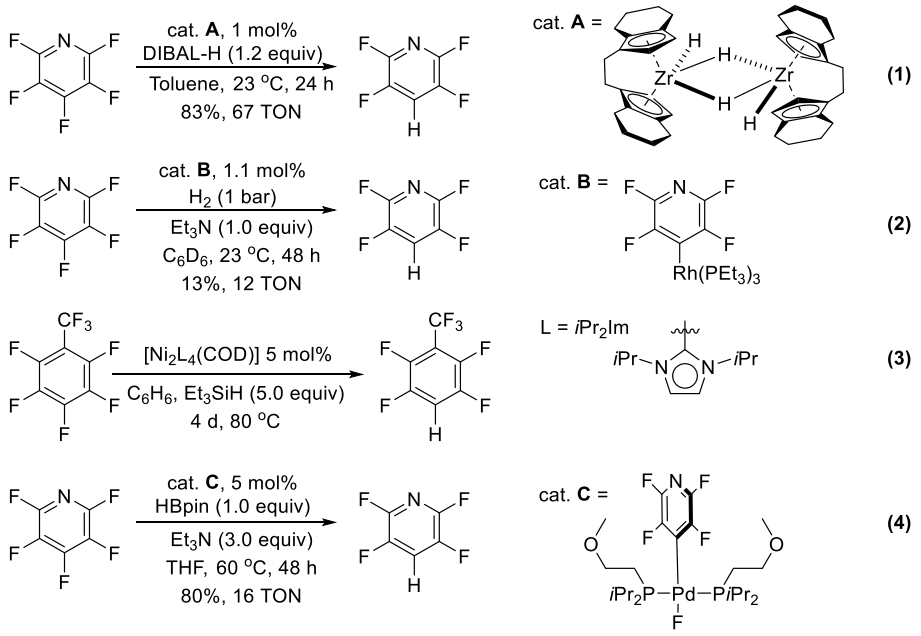
Scheme 1.3 Current fluorination strategies

To circumvent the difficulties associated with selective fluorination of an arene, selective defluorination of perfluoroarenes has emerged as an alternative strategy to access polyfluoroarenes. This is a particularly attractive approach because perfluoroarenes are an abundant and a cheap class of chemicals which are produced on large scale, primarily using the halogen exchange (Halex) process.[15] Furthermore, every position is potentially substitutable, which gives the perfluoroarene great potential for synthesis. Arguably, selective removal of fluorines *via* hydrodefluorination would give us the opportunity to use widely available

perfluoroarenes as starting materials to create expedient syntheses of partially fluorinated aromatics, and furthermore, allow the perfluoroarene to be used as the synthetic hub to connect the rest of the molecule, as opposed to a terminating group.

1.3 Introduction for hydrodefluorination

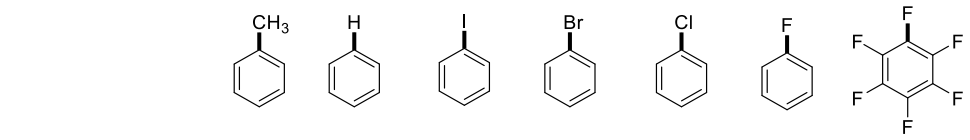
As stated in section 1.2, the hydrodefluorination (HDF) of perfluoroarenes had emerged as an alternative approach to selective fluorination. Significant efforts have been devoted towards the development of HDF reactions under catalytic conditions (Scheme 1.4).[16] Among the most common catalytic systems, the use of metal-hydrido complexes,[17] catalysts based on Rh,[18] Ni,[19] Pd,[20] and Au[21] are prevalent in the literature and some selected examples are shown in Scheme 1.4 below.



Scheme 1.4 Some transition metal catalyzed hydrodefluorination reactions

In stark contrast to the relatively difficult C–F bond breakage, other C–X bonds (X = I, Br, Cl) are much more easily reduced. For instance, the rate of lithium-halogen exchange of C_{aryl}-X bonds decrease from I > Br > > Cl and when X= F, the exchange is not feasible.[22] The

difficulty of C–F reduction arises primarily from the enormous C–F bond strength (145 kcal/mol for C_6F_6)[23] and the short bond length (1.32 Å for C_6F_6)[24] of C_{aryl}–F (Scheme 1.5). The primary result is that the C–F bond is both kinetically and thermodynamically robust and cleavage of the bond has been a difficult struggle to overcome.[16b]



Bond energy (kcal/mol)	104	113	67	84	97	117	145
Bond length (Å)		1.1	2.14	1.91	1.76	1.35	1.32

Scheme 1.5 Comparison of bond strength and bond length

Further complicating the matter, even if the robust C–F bond is ruptured, most catalytic HDF systems suffer from extremely low turnover number (TON). Often this is due to formation of a strong metal–fluorine bond during the catalytic cycle, which results in sluggish turnover. One established way to overcome such catalyst deactivation is to use a fluorophilic silyl- or aluminum-hydride. The hydride bearing atom facilitates the catalyst turnover by acting as a sacrificial fluorophile[25] which can form a strong Si– or Al–F bond. Consequently, this liberates the catalyst from the thermodynamic well and increases the overall exothermicity of the reaction. Nonetheless, most metal catalyzed HDF reactions still suffer from low TONs.[16b]

1.4 Outer sphere electron transfer as a way to reduce C–X bonds

It is well known that perfluoroarenes are thermodynamically and kinetically inert, and this has slowed development of novel C–F functionalization chemistry. For instance, separate oxidative addition reactions of (η^5-C_5H_5)Rh(PH_3) to a C–F bond and to an *ortho*-C–H bond of 1,4-difluorobenzene occurs with energy barriers of 33.3 kcal/mol and 9.4 kcal/mol respectively.[26] However, another consequence of addition of fluorines is that they possess a relatively low lying LUMO when compared to the corresponding H-arenes. For instance, the reduction potential of

C_6H_6 is more negative ($E_{1/2red}$ = −3.42 *vs.* SCE) than its perfluoro analog, C_6F_6 ($E_{1/2red}$ = −2.81 *vs.* SCE).[27] Therefore, it is expected that C_6F_6 accepts an electron easier than its protonated counterpart,[28] and thus, can form the corresponding metastable radical anion. This radical anion may undergo non-productive back electron transfer or productive fluoride fragmentation and extrusion. The latter would result in an aryl radical that could be functionalized or reduced, and thus is an attractive approach that circumvents the aforementioned problems of processes that rely on oxidative addition.

In general, the LUMO to which an electron can be added is the π* orbital of the haloarene. Upon formation of the radical anion, in order for the C–X bond to be fragmented, an electron transfer should take place from the π* to the σ* orbital of the desired C–X bond. However, for the planar π-type radical anion, monomolecular fragmentation is symmetry forbidden (Figure 1.2a), because the two orbitals are orthogonally situated. The effect of the leaving halogen on the fragmentation is shown in Figure 1.2b. Sterically larger and less electronegative atoms lower the σ* energy and consequently promote an easier fragmentation (i.e., when X= I the fragmentation becomes essentially barrierless).

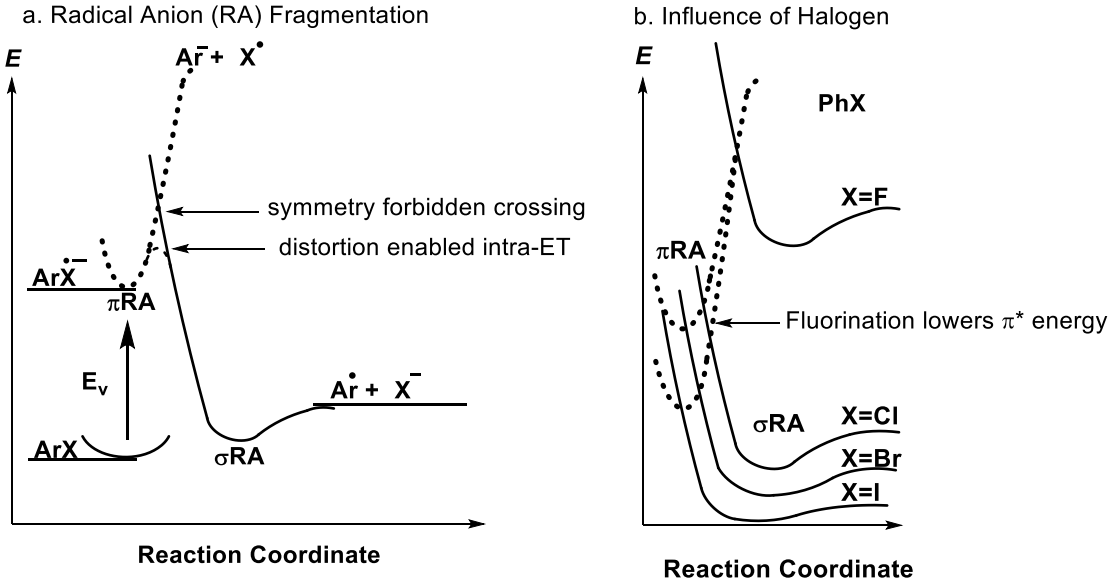
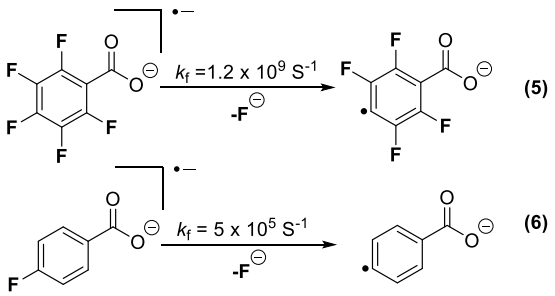


Figure 1.2 Energy diagrams for radical anion fragmentation

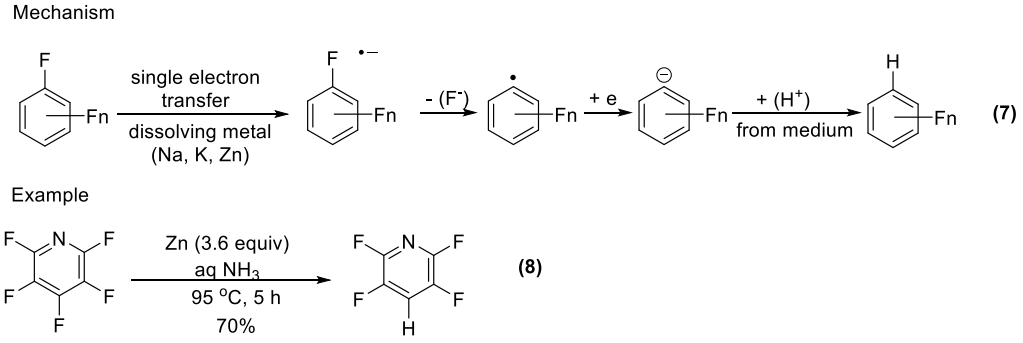
When polyhaloarenes are considered the π* energy will be lowered as depicted in Figure 1.2b. As a consequence, the barrier to the fragmentation mediated by electron transfer should become even more significant for polyfluoroarenes compared to the corresponding monofluoroarenes. However, this is not what is actually observed. In a comprehensive study of a symmetry forbidden fragmentation of different mono- and polyfluorobenzoates which was carried out by Konovelov and Shteingarts, revealed that the rate constants for fragmentation show an increase of about four orders of magnitude when the ring is perfluorinated over the monofluorinated benzoate (Scheme 1.6).[29] This observation is further perplexing because of the fact that the C–F bond dissociation energy (BDE) for fluorobenzene is 117 kcal/mol, while that for hexafluorobenzene is 145 kcal/mol.[29] The phenomenon can be explained by the greater propensity of perfluorobenzoate radical anion to distort out of the plane of the aryl ring when compared to the monofluorobenzoate radical anion. The consequence of distortion is a significant orbital mixing of the π* and σ* orbitals,[30] and ultimately more facile C–F fragmentation.



Scheme 1.6 Radical anion fragmentation rates of poly- and monofluorobenzoates

The most common reductive defluorination of perfluoroarenes has been accomplished *via* the transfer of solvated electrons with dissolving metals (Scheme 1.7, eq 2) and extensively studied by Shteingarts.[29, 31] This initially gives rise to a metastable nonplanar radical anion which

then can undergo a unimolecular fluoride fragmentation to produce a perfluoroaryl radical. This radical is reduced to its anion *in situ* to form the HDF product after protonation of the anion from the medium (eq 7). This chemistry, while synthetically limited, does provide strong evidence for the feasibility of single electron transfer to perfluoroarenes as an alternative way of accessing a reactive intermediate and potentially functionalizing the perfluoroarene.

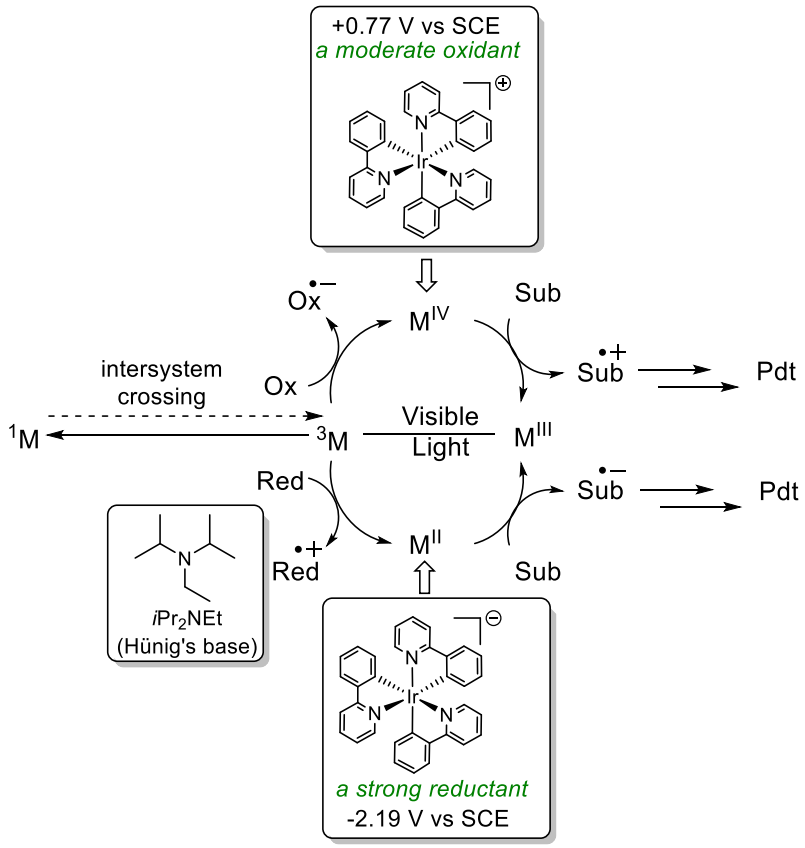


Scheme 1.7 Hydrodefluorination by solvated electrons

1.5 Photocatalysis as a way to perform outersphere electron transfer

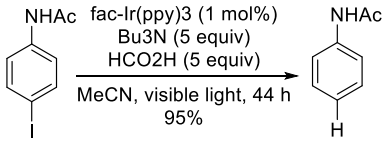
While the dissolving metal reductions of perfluoroarenes indicate the feasibility, they are not very compatible with many functional groups. One alternative way of performing outersphere electron transfer to a haloarene is to use photocatalyst. The beauty of photocatalysis as a way to transfer an electron is the ability to make reactive species in a controlled manner by generating the reactive species *in situ,* and only in a catalytic amount. Upon absorption of a photon in the visible region an electron is promoted from a metal centered t_{2g} orbital to a ligand centered π^* orbital, thus termed as metal-to-ligand charge transfer (MLCT). The initially occupied singlet MLCT state (^{1}M) then undergoes a rapid intersystem crossing to a lower energy, and longer lived, triplet state (^{3}M). This triplet state is sufficiently long lived to engage in a bimolecular electron transfer reaction (i.e, excited-state lifetime, τ = 1900 ns for *fac*-Ir(ppy)$_3$ catalyst and τ = 1100 ns for Ru(bpy)$_3^{2+}$ catalyst).[32] The absorption of the photon can induce what

would be otherwise both endergonic reductions and oxidations. Even though, the overall complex is neutral at this point, the electron transfer effectively oxidizes the metal center by one oxidation state and the ligand framework is reduced by one oxidation state. The metal center acts as an oxidant with molecules, while the ligand acts as a reductant. Therefore, the complex can simultaneously act as both a better oxidant and a better reductant than its ground state molecule. This can be further explained by reduction potential numbers. When *fac*-Ir(ppy)$_3$ is considered, the excited state molecule is more oxidizing ($E_{1/2}^{*II/I}$ = +0.31 V *vs.* SCE) than its ground state ($E_{1/2}^{II/I}$ = -2.19 V *vs.* SCE). Meanwhile, the excited catalyst is more reducing ($E_{1/2}^{III/*II}$ = -1.73 V *vs.* SCE) than its ground state reduction potential ($E_{1/2}^{III/II}$ = +0.77 V *vs.* SCE) as well (Scheme 1.8).



Scheme 1.8 Generic catalytic cycles for photocatalysis showing oxidative and reductive quenching pathways

The work done by Yoon,[33] MacMillan,[34] Stephenson[35] and others[27, 36] popularized the field of photoredox chemistry as a tool for organic synthesis. Stephenson, in 2012, demonstrated the reduction of C_{aryl}–I bond in the presence of *fac*-Ir(ppy)$_3$ photocatalyst (Scheme 1.9).[37] Knowing the photoredox catalyst's ability to perform 1-electron chemistry cleanly and selectively, we set out to investigate the utility of photocatalysis to answer the difficult problem of C–F derivatization.



Scheme 1.9 Stephenson's photocatalytic C–I reduction

Even though, Stephenson's iodide reduction shows the feasibility of photocatalysis as a way to reduce aryl–iodide reduction, it remained to be seen whether photocatalysis could serve to break the much stronger C–F bond (>2x C–I BDE). Further, questions remained beyond feasibility, such as selectivity. With multiple C–F bonds, the chemistry is only useful if it generates products selectively. If successful, would it be possible to utilize the intermediate radical for further couplings beyond just the reduction? With these questions in mind we initiated our studies.

CHAPTER II

PHOTOCATALYTIC HYDRODEFLUORINATION OF PER- AND POLYFLUOROARENES

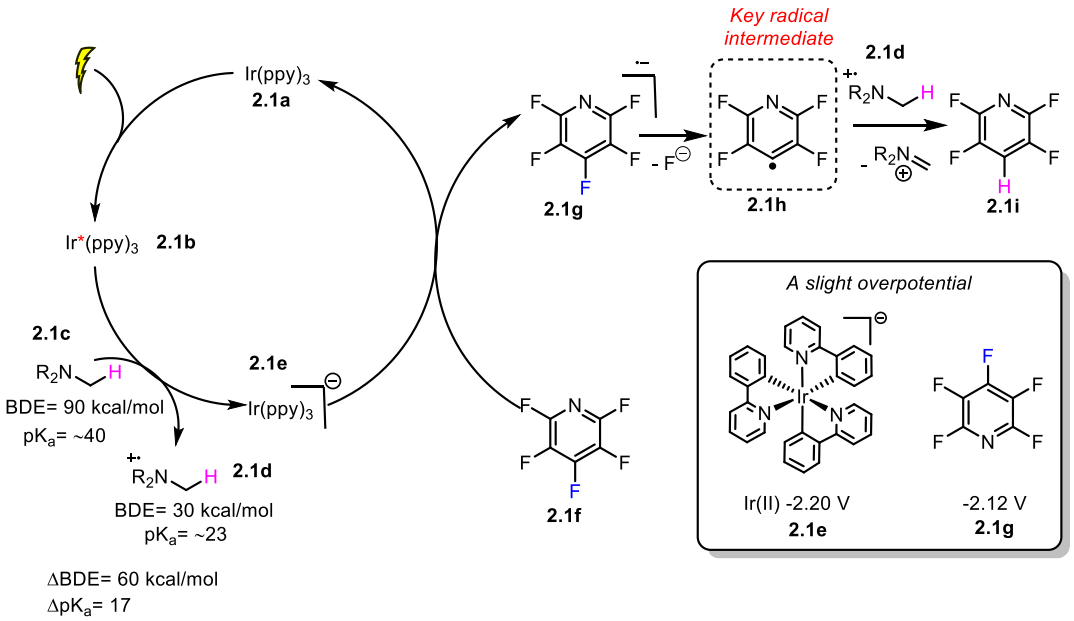
2.1 Development of the photocatalytic hydrodefluorination (photo-HDF) reaction

We started investigating the feasibility of C–F reduction using visible light photocatalysis as an outersphere electron transfer strategy. We envisioned that *fac*-tris[2-phenylpyridinato-C^2,*N*]iridium(III) [*fac*–Ir(ppy)$_3$], which is a coordinatively saturated 18-electron complex, and is a potent reductant (-2.19 V *vs.* SCE $Ir^{II/III}$)[38] could transfer an electron from its reduced state to the desired perfluoroarene. The stability of the complex also comes from the fact that the ligands are bidentate, and therefore, they are far less likely to dissociate. Consequently, the formed perfluoroaryl radical anion would lead to a fragmentation of the C–F bond, forming the perfluoroaryl radical upon extrusion of the fluoride. Ultimately the desired reduction product would then arise as a result of a hydrogen atom transfer to the perfluoroaryl radical. This mode of reactivity is significantly different from the dissolving metal reductions of a C–F bond (described in Chapter 1) where the radical is subsequently reduced to its anion. Furthermore, the outer sphere nature of the electron transfer might avoid the problematic catalyst–fluoride

intermediates and lead to high TONs. The ability of photocatalysts to generate an excellent H-atom donor during the reductive quenching process is also noteworthy.

We hypothesized the following mechanism (Scheme 2.1). Upon absorbing a photon in the visible region[27, 39] the ground state photocatalyst (**2.1a**) is promoted to an excited singlet state[38] which rapidly undergoes intersystem crossing to give a long lived triplet state (**2.1b**). The photoexcited species bear a remarkable property of being both more oxidizing ($E_{1/2}^{II/I}$ = -2.19 V *vs.* SCE) and more reducing ($E_{1/2}^{III/*II}$ = -1.73 V *vs.* SCE) than the ground state species ($E_{1/2}^{III/II}$ = +0.77 V *vs.* SCE).[32] A successful quenching of the excited photocatalyst with a reductive quencher will generate the reduced photocatalyst which then can transfer its electron to a substrate molecule which has a well-matched reduction potential.

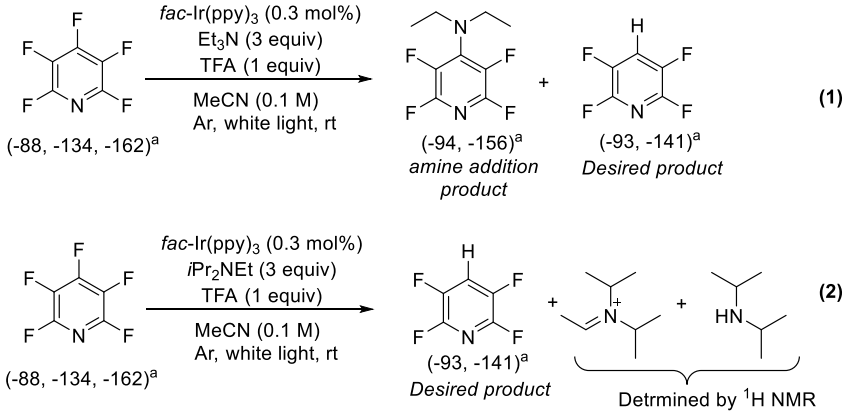
We decided to commence our search using *fac*-Ir(ppy)$_3$ as the catalyst and pentafloropyridine as the model substrate, because of the slight overpotential between the reduced photocatalyst (-2.19 V *vs.* SCE $Ir^{II/III}$)[38, 40] (**2.1e**) and the perfluoroarene (V = −2.12 *vs.* SCE) (**2.1f**).[41] We expected that a simple amine (**2.1c**) could serve as an electron donor (i.e. reductive quenching), which results in an amine radical cation (**2.1d**) and a reduced photocatalyst (**2.1e**). This event gives rise to a reactive amine radical cation wherein the αC–H bond is significantly weakened compared to the parent amine and consequently is also significantly acidified. At this point we postulated an outer sphere electron transfer would take place from **2.1e** to the fluoroarene (**2.1f**) to generate a perfluoroaryl radical anion, **2.1g**. Subsequent fluoride extrusion forms a perfluoroaryl radical (**2.1h**) followed by an H-atom abstraction. The H-atom donor is either the amine, or amine radical cation, and both lead to the desired reduced product (**2.1i**).



Scheme 2.1 Plausible mechanism for the photo-HDF reaction

We started our investigation of the photo-HDF reaction with pentafluoropyridine and *fac*-tris[2-phenylpyridinato-C^2,*N*]iridium(III) [*fac*–Ir(ppy)$_3$] as the catalyst in MeCN. Initially, we carried out two parallel reactions to pick the best acid/base combination. For that we chose 1) a mixture of Et_3N and trifluoroacetic acid (TFA) and a 2) mixture of *N*,*N*-diisopropylethylamine (*i*Pr_2*N*Et or Hünig's base) and TFA. The reactions were irradiated with white light generated by a CFL bulb located ~2 inches from the NMR tube. The reactions were monitored *via* ^{19}F NMR. Later we started using blue LED lights (Solid Apollo, 18 LEDs/feet) as the light source, since only the blue portion of the spectrum contains photons of the appropriate energy to excite the catalyst. Qualitative evaluation of the crude NMRs (both ^{1}H and ^{19}F NMR) showed us the formation of the desired product in both reactions. The product formation was further confirmed by comparing the crude reactions with the commercially available 2,3,5,6-tetrafluoropyridine. When TFA was used with Et_3N, *N*-fluoroarylated product was observed by both ^{1}H and ^{19}F NMR along with the desired HDF product (Scheme 2.2, eq 1). In contrast, when *i*Pr_2NEt/TFA was

used, no *N*-substitution was observed. Due to the cleaner reaction obtained with *i*Pr_2NEt/TFA system (eq 2), it was selected for further optimizations.



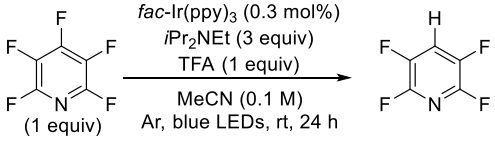
[a] Determined by ^{19}F NMR, ^{19}F NMR chemical shifts (in ppm) are shown in parentheses

Scheme 2.2 Initial results obtained for the photo-HDF reaction

We then evaluated the loadings of both acid and base. The results revealed that the reaction become slower with super stoichiometric amounts of TFA (Table 2.1). Alternatively, more amine seems to accelerate the reaction presumably both by accelerating reductive quenching of the excited photocatalysts and by increasing the probability of H-atom abstraction.

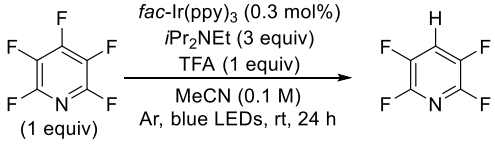
Table 2.1 Optimization of the acid and base equivalents

Screeening of TFA equivalants



entry	equiv of TFA	conversion %
1	0.2	64%
2	0.5	65%
3	1.0	99%
4	2.0	44%

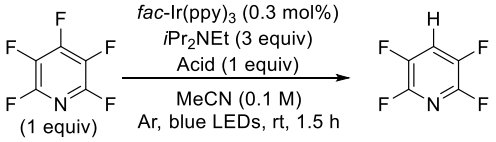
Screeening of base equivalants



entry	equiv of *i*Pr_2NEt	conversion %
1	0.5	0%
2	1.2	1%
3	2.0	53%
4	3.0	100%

In order to select the best acid for the reaction we started looking at the effect of different acids in the reaction (Table 2.2). For that we chose several organic acids with a range of p*K*a values[42] to investigate the possibility of a Brønsted correlation between pK_a and rate of the reaction. When compared to stronger acids such as TFA and TsOH, weaker formic acid led to greater conversion at 1.5 h. Meantime, it is worth noting that these acids contain varying amounts of water. Therefore, it may not be completely fair to directly compare them. However, when no acid was included in the reaction (entry 5) only a very subtle effect on the rate was observed, and in fact it cleaned up the reaction to a slight extent (Table 2.2). Therefore, we decided to carry out rest of the optimizations without any acid present.

Table 2.2 Effect of acid in the photo-HDF reaction



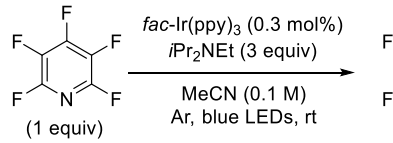
entry	Acid	pKa (H_2O)	conversion %
1	HCOOH	3.77	83%
2	CH_3COOH	4.76	51%
3	*p*-toluenesulfonic	-2.8	58%
4	TFA	-0.25	43%
5	No acid	-	78%

After obtaining the above preliminary results, we turned our attention to a more systematic optimization of the photo-HDF reaction. Apart from *fac*-Ir(ppy)$_3$, we tested the reactivity of two other photocatalysts which have substantially lower reduction potentials compared to *fac*-Ir(ppy)$_3$ (Table 2.3). Remarkably, Ru(bpy)$_3$Cl$_2$ (V = −1.33 *vs.* SCE) and Ru(bpm)$_3$Cl$_2$ (V = −0.91 *vs.* SCE) led to the formation of some product, albeit Ru(bpm)$_3$Cl$_2$ gave only a trace amount, but was both reproducible and detectable by ^{19}F NMR. These low, but real conversions from far less reducing photocatalysts are impossible to explain by the reduction potentials alone (entry 2 and 3). This was puzzling but, gave us some insights about the

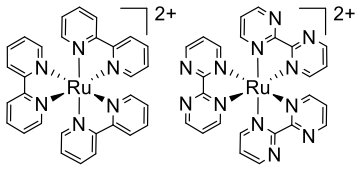
dependence of electron transfer on factors other than the reduction potential of the catalyst. Zhang and co-workers have extensively studied this feature in their HDF reaction using pyrene-based photocatalysts.[43] They have shown that an aromatic donor-acceptor interaction between an electron rich pyrene catalyst (as the electron donor) and an electron poor perfluoroarene (as the electron acceptor) promotes an electron transfer against unfavorable underpotentials. This clearly shows that the existence of features other than the reduction potential on electron transfer.

Next, we carried out some control experiments (entry 4 and 5). A reaction was set up with no photocatalyst and another reaction was carried out in the dark. Both resulted in no conversion, and indicate the photocatalytic nature of the reaction. Similarly, a reaction was performed without degassing under an air atmosphere and we were not able to see any product formation. Consequently, we included a degassing step of the reaction under argon before placing it in the light bath. This supports the idea of a reductive quenching of the photocatalyst by an amine in the productive reaction. In other words, when O_2 is present it out competes the amine in the excited state quenching event,[44] effectively oxidatively quenching the photocatalyst, and stopping the HDF-reaction sequence.

Table 2.3 Reaction with other photocatalysts and control experiments



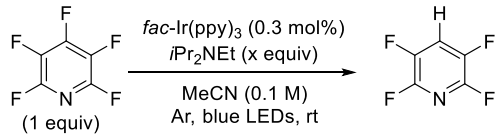
entry	modification	time	conversion %
1	None	24 h	100%
2	$Ru(bpy)_3Cl_2$ instead of $Ir(ppy)_3$	24 h	37%
3	$Ru(bpm)_3Cl_2$ instead of $Ir(ppy)_3$	24 h	2-3%
4	without degassing	24 h	0%
5	no cat. or in dark	24 h	0%



The effect of the amount of the *i*Pr$_2$NEt in the reaction was examined and has been presented above. However, we again conducted a more detailed and systematic study on the

amine equivalents (Table 2.4). Looking at an early time point, the results showed an increase of the initial rate of the reaction with increasing amounts of amine until 2 equiv of amine, and then upon the addition of more amine, the reaction actually slowed. However, all the reactions reached completion, albeit formation of byproducts was observed when a large excess of amine was used. Given the ability of achieving clean conversion with 2.0 equiv of *i*Pr_2NEt, we decided to use that amount in further studies.

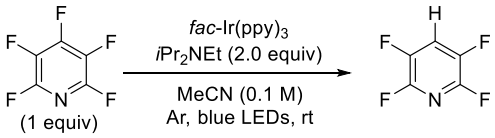
Table 2.4 A detailed study of the amine equivalents in the HDF reaction



entry	*i*Pr_2NEt equiv	conversion % t= 0.5 h	t= 2 h	t= 6 h	t= 22.5 h
1	1.2	32%	63%	91%	100%
2	2.0	35%	61%	96%	100%
3	3.0	27%	55%	100%	100%
4	5.0	23%	57%	100%	100%
5	10.0	8%	59%	100%	100%

Next, we turned our attention to the catalyst loading (Table 2.5). Reactions with catalyst loadings ranging from 0.05 to 0.25 mol% showed a dependency of rate of the reaction on the amount of the catalyst. Because of that, ultimately, we started 0.5 mol% of *fac*-Ir$(ppy)_3$, which was a saturated solution of *fac*-Ir$(ppy)_3$ in MeCN.

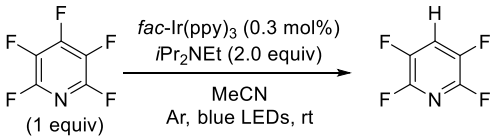
Table 2.5 Effect of the catalyst loading



entry	catalyst mol%	conversion % t= 0.5 h	t= 2 h
1	0.05	5%	12%
2	0.125	25%	43%
3	0.25	47%	83%

Finally, we looked at the effect of the substrate concentration on the rate of the reaction (Table 2.6). The reactions were set up with five different concentrations ranging from 0.075 M to 0.35 M. The relative ratios of other reactants were kept constant. To the first approximation a 5-fold substrate concentration increase results in a ~2-fold rate increase. However, given that the catalyst loading (rather than concentration) is held constant (actually a ~5-fold conc. increase) and the demonstrated catalyst dependency, it appears that the reaction rate is pseudo-zero order in substrate. Based on the above data, the rate determining step (RDS) of the reaction seems to be the reductive quenching of the catalyst by the amine.

Table 2.6 mmol of the product formed as a function of reaction concentration



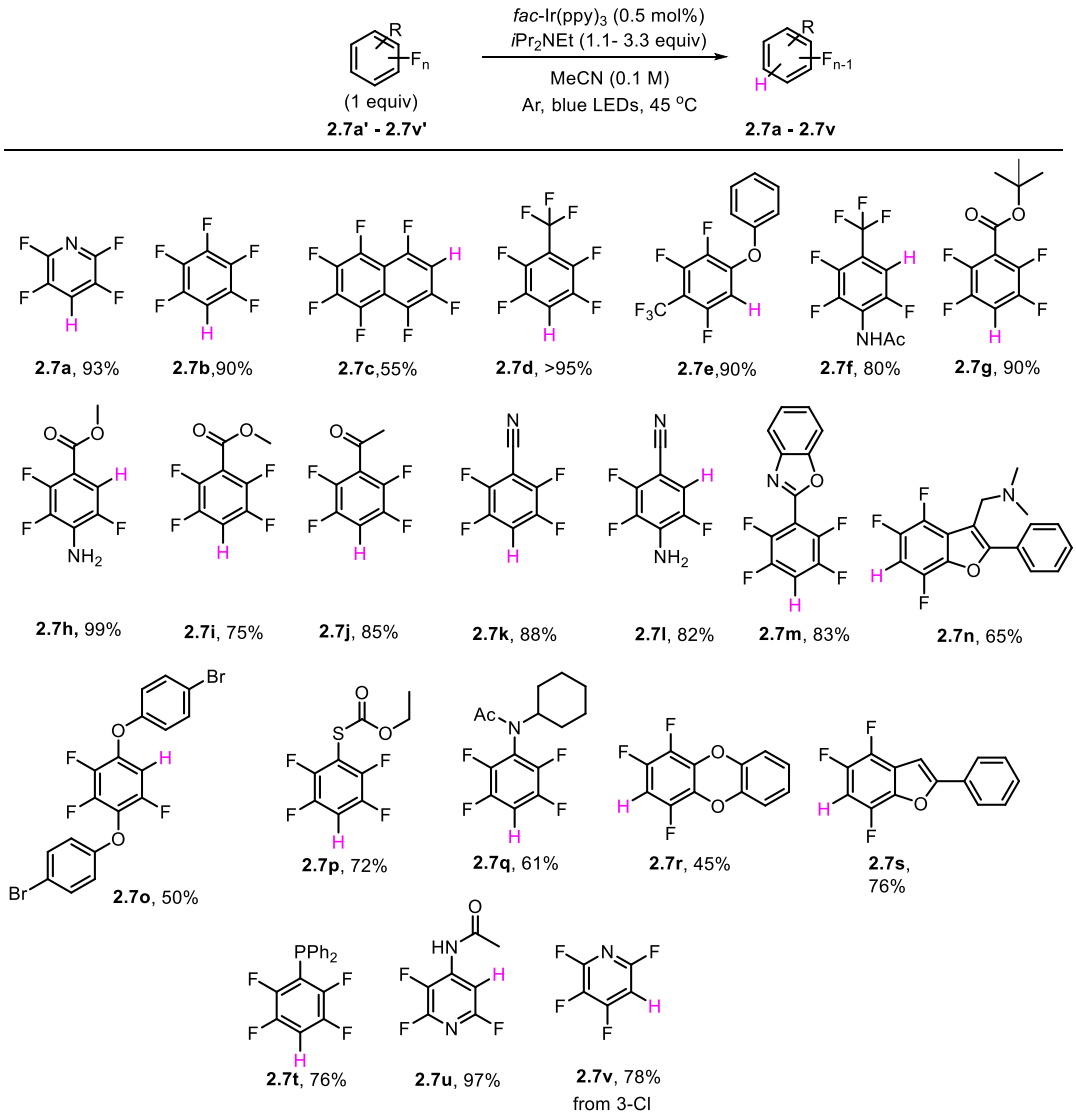
entry	reaction concentration	conversion mmol t= 0.5 h	t= 6 h
1	0.075 M	0.015	0.050
2	0.10 M	0.018	0.063
3	0.15 M	0.017	0.044
4	0.20 M	0.022	0.058
5	0.35 M	0.032	0.070

After knowing the influence of each reagent in the photo-HDF reaction we started to investigate the scope of the reaction using 0.1 M substrate, 1.1−3.3 equiv of *i*Pr_2NEt, and 0.5 mol% of photocatalyst. Meanwhile, we encountered the problem of keeping the temperature of the light bath constant. Due to the heat generated by LEDs, or more specifically resistive heating from the wiring, which resulted in a warming of the light bath, it was challenging to maintain the reaction temperature at room temperature. In addition, uncontrollable variations in the house air temperature often led to temperature swings from 20 °C to 26 °C. In order to avoid this problem and to maintain a consistent reaction temperature we decided to use a heated water bath which was wrapped with blue LEDs. The temperature was maintained at 45 °C with the aid of a sand bath connected to a thermostat. The complete experimental setup is described in the experimental section.

First, we investigated the ability to perform mono photo-HDF. Under these conditions the scope of the reaction was broad. Both activated (**2.7a'**, **d'**, **f'**, **g'**, and **i'**-**k'**) and un-activated (**2.7b'** and **c'**) perfluoroarenes engaged in the reaction and gave the products in good to excellent yields. Generally, HDF of less activated arenes was slower than the activated arenes, and more amine (i.e., 3.3 equiv) was needed to speed up the reaction. The reaction had a remarkable functional group tolerance including CF_3 (**2.7d**-**f**), ketones (**2.7j**), esters (**2.7g-i**), nitriles (**2.7k**-**l**), and oxazoles (**2.7m**). A substrate containing an aliphatic amine **2.7n'** was subjected to the reaction and resulted in a satisfactory yield. This is somewhat remarkable because of the role that tertiary amines play in photocatalytic cycle. In perfluoropyridine systems such as pentafluoropyridine, the reduction happens at the most activated 4-F position to yield 2,3,5,6-tetrafluoropyridine (**2.7a**). However, complementary 2,3,4,6-tetrafluoropyridine (**2.7v**) can be synthesized by starting with the corresponding 3-chloro-2,4,5,6-tetrafluoropyridine. In the case of **2.7v'**, (Ar-Cl), due to the fact that the C−Cl σ* is lower in energy, the fragmentation occurs at the chlorinated carbon. Perfluoroarenes substituted with electron releasing amino, alcohol, or

thiol groups proved to be sluggish or unselective substrates. For instance, when pentafluoroanisole was used as the starting arene, a sluggish reaction was observed along with the products generated from *ortho*, *meta*, and *para* reductions. However, when these inactivating groups were modified by the appropriate functional groups (i.e., a phenyl ether instead of methyl ether), the sluggish substrates became quite reactive and underwent facile reaction (**2.7o**). Modulation of the substrates electronically also activated them towards the HDF. Electron releasing thiols became active after conversion to the thiocarbonate (**2.7p**) and similarly amines were activated by acylation (**2.7u**). Other ring functionality can also serve to activate substrates with electron releasing groups (**2.7e', f', h', l'** and **u'**). Highly fluorinated phosphines (**2.7t'**), which are an important class of ligands for several catalytic transformations,[45] also underwent HDF, which might provide a facile method of fine-tuning of the electronics of a potential ligand. Furthermore, we synthesized several fused arenes with C–O linkages which are prevalent in material science applications (**2.7n'**, **r'** and **s'**).[46] All of those displayed smooth HDF. This would allow synthetic chemists to use the C_{aryl}–H bond in the product as a handle to further elongate the molecule *via* C–H activation and cross-coupling reactions, which is chemistry that has been established by a number of groups.[47]

Table 2.7 Scope of the mono hydrodefluorination

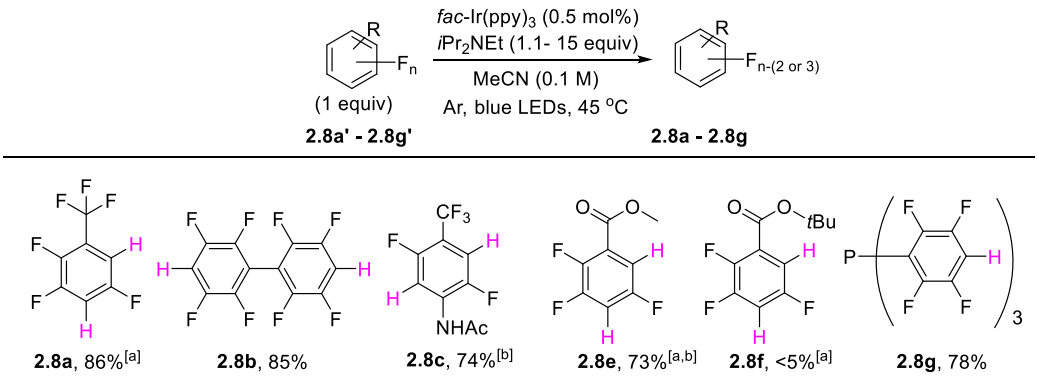


Given that radical anion fragmentation usually occurs preferentially with heavier halogens which possess weaker C–X bonds, it is an interesting observation that the bromines of **2.7o'** almost completely survive the reaction, with only minor amounts of C–Br reduction observed. In other words, the starting dibromide underwent preferential C_{aryl}–F reduction rather than C–Br reduction.[48] This selectivity can be best explained by relative energies of the orbitals of the fluoroarene and the bromoarene moieties of the molecule. The LUMO (π* orbital of the haloarene) of the molecule lies on the fluoroarenes, thus the electron from the reduced

photocatalyst preferentially transfers to the LUMO which is located on the fluroarene moiety. This example serves as a good reminder that electron transfer can be selective and the simple presence of heavier atoms should make one assume that it will be incompatible.

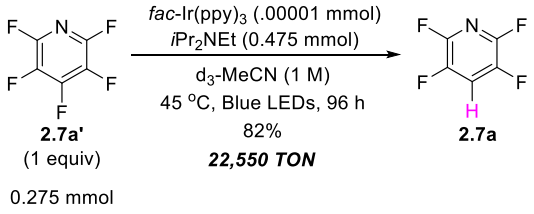
Next, we turned our attention to investigate the feasibility of performing a second reduction event (Table 2.8). We were pleased to see both di- and even tri-HDF events to afford products that would be difficult to access by any other means. Among the substrates tried, the rates between the first and sequential reductions were sufficiently different to be able to stop at the desired HDF product (i.e., either *mono*- or *di*-HDF product). Two exceptions were tri(pentafluorophenyl) phosphine and the decafluorobiphenyl where we isolated tri and di HDF products respectively (**2.8b** and **2.8g**). In the cases where the difference in rate constants for mono- and di-reduction is substantial, selectivity can be controlled by the equivalents of amine used and by careful monitoring of the reaction. Octafluorotoluene undergoes ortho, para di-HDF, leaving the benzylic fluorines intact (**2.8a**). While the regioselectivity of the HDF event is primarily dictated by the electronics of the perfluorarene,[49] the rate difference in the di-HDF of the methyl (**2.8e**) and *tert*-butyl esters (**2.8f**) is substantial and suggests that there is a steric contribution. Finally, perfluorotriphenyl phosphine undergoes smooth conversion to the tri-HDF product (**2.8g**) which allows the direct synthesis from commercially available phosphine. Other known procedures for the synthesis of this substrate start with relatively expensive 1-Br-2,3,5,6-tetrafluorobenzene (which is itself a derivatized HDF product) and form the Grignard reagent and react it with PBr_3.[50] Some slower substrates needed a large excess of amine to undergo HDF in a satisfactory rate. For instance, **2.8c** and **2.8g** were synthesized using 6 equiv and 15 equiv of *i*Pr_2Net, respectively.

Table 2.8 Di- and tri-HDF



[a] ^{19}F NMR yield, [b] 42 h.

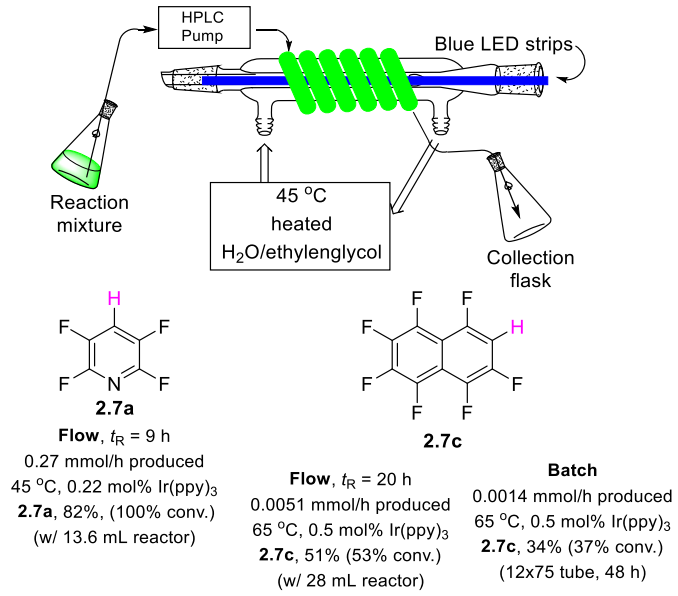
As described in chapter I, extremely low TON is one of the major drawbacks associated with the existing HDF reactions. The best catalytic TON achieved for pentafluoropyridine was only 67 TON[51] and for any type of HDF substrate it was only a 1000 TON.[21] To demonstrate the robustness of the photo-HDF, due in part to the 18-electron, coordinatively saturated photocatalyst, we designed an experiment to evaluate the TON of *fac*-Ir(ppy)$_3$ using pentafluoropyridine as the substrate. Generally, all of our reactions used low catalyst loading (i.e., at 100 % conversion, TON= 200). However, the 0.5 mol% loading we used was out of convenience and did not test the robustness of the catalyst. Sequential addition of a mixture of the substrate and the amine to a solution of catalyst in MeCN was carried out over four days under normal operating conditions. We were not able to find an endpoint. The reaction was quenched after four days not because of the catalyst demise, but because the formation of byproducts began to increase. At this point, we were able to obtain a yield of 82% and to achieve an unprecedented TON of 22,550.[16b, 51-52] Building off our work, the Zhang group has shown that pyrene based dye is able to accomplish a photo-HDF with a >24,000 TON.[43]



Scheme 2.3 Unprecedented TON obtained for *fac*-Ir(ppy)$_3$ in the HDF reaction with pentafluoropyridine

Given that the use of partially fluorinated aromatics in numerous applications as discussed in chapter I, obtaining larger quantities of these materials is necessary. Conversely, one major criticism of the photocatalysis is the scalability. Typically, during photochemical processes photons are absorbed very near the surface, and consequently, the light source fails to irradiate the entire volume of the reaction solution. Consequently, upon scaling up a photochemical reaction the path length of the light increases as the volume of the reaction vessel increases. This often leads to a phenomenon called photo-starvation (or light-starvation)[53] where the light source fails to irradiate the entire volume of the solution. Shortening the path length by decreasing the diameter of the flask should increase the flux of photons throughout the vessel and thereby increase the effective concentration of active catalyst, and thus the rate of the reaction. We fabricated a homemade photoflow reactor where fluoroalkoxy polymer tubing was used as the reaction vessel with a very small inner diameter (see experimental section for details of fabrication of the reactor and the reaction details). Both pentafluoropyridine and octafluoronapthalene substrates were subjected to the photoflow reaction and the results are presented in Scheme 2.4. Pentafluoropyridine underwent smooth conversion to its mono-HDF product at a rate of 0.27 mmol/h (978 mg/24 h). Under standard batch reaction conditions octafluoronapthalene was sluggish and never reached complete conversion. Interestingly, it did not reach completion in the flow reactor either, but we detected a 3.75x rate enhancement when compared to the corresponding batch reaction. These results strongly suggests that the HDF

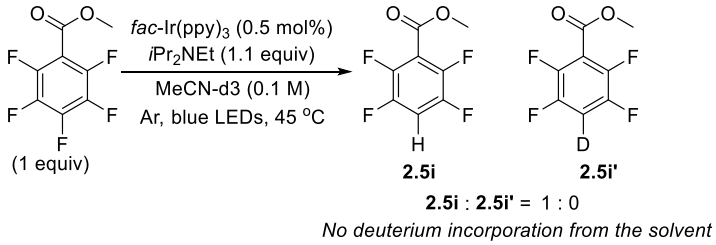
method we developed is amenable to flow method development to obtain large quantities of product when desired.



Scheme 2.4 Flow reactor setup for the HDF reaction

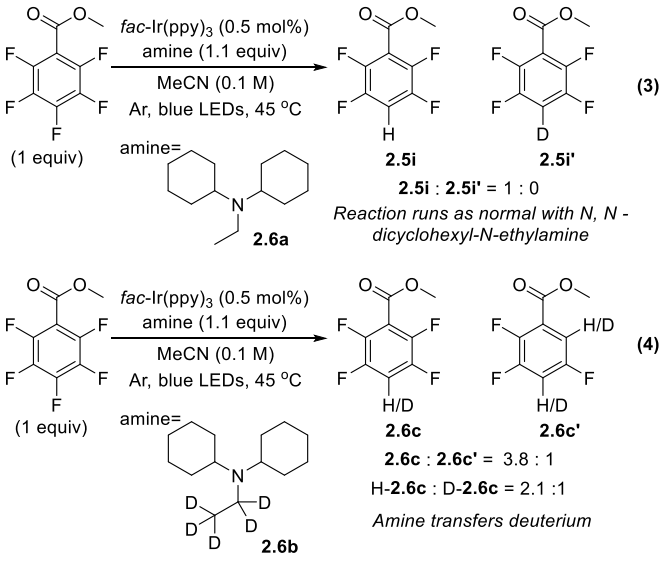
Next, we wanted to study the mechanistic details of the reaction. To determine the source of the H-atom, three separate NMR reactions were carried out using methyl 2,3,4,5,6-pentafluorobenzoate as the perfluoroaryl starting material. Those were 1) an HDF-reaction with methyl-2,3,4,5,6-pentafluorobenzoate and *i*Pr$_2$NEt in MeCN-d$_3$ to see if the solvent served as the H-atom source, 2) an HDF reaction using *N*,*N*-dicyclohexyl-*N*-ethylamine, and finally 3) an HDF reaction using *N*,*N*-dicyclohexyl-*N*-d$_5$-ethylamine to evaluate the H/D transfer ability of amine. All the reactions were monitored by both ^{19}F, ^{1}H NMR. GC-MS was used to detect the molecular ion of the product/s. ^{19}F NMR showed the formation of a single product, which matched with the data obtained for **2.5i** (Scheme 2.5). Relative integrations of the aromatic H and the methyl signal of ^{1}H NMR also matched with the above observation. Therefore, we concluded that no deuterium incorporation from the solvent had occurred.

When *N,N*-dicyclohexyl-*N*-ethylamine was used as the amine in MeCN-d_3 and methyl-2,3,5,6-tetrafluorobenzoate was detected as the major product by ^{19}F NMR, ^{1}H NMR and GC-MS, consistent with the normal HDF reaction with no incorporation of deuterium.



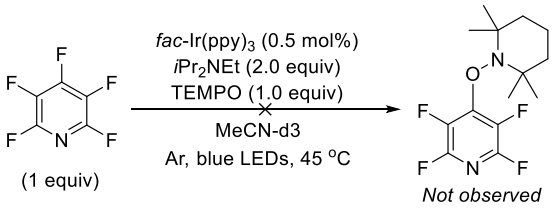
Scheme 2.5 HDF of methyl-2,3,4,5,6-pentafluorobenzoate in MeCN-d3

When the reaction was performed using an analogous deuterium labeled amine, deuterium was incorporated (methyl-2,3,5,6-tetrafluorobenzoate (H/D-**2.6c**) with a 2.1/1 H/D ratio, which was detected as the major products along with di-HDF products (H/D-**2.6c'**) by ^{19}F NMR, ^{1}H NMR and GC-MS. This result confirms that the amine as the source of the H/D-atom but also reveals that all α-C-Hs can be transferred.



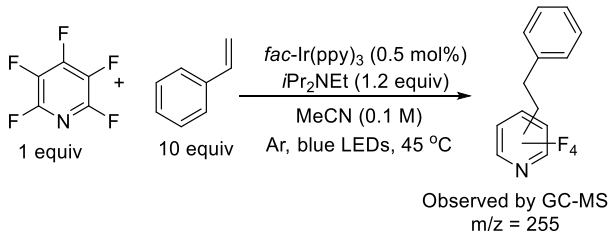
Scheme 2.6 Deuterium labeling experiment to identify the source of the H-atom in the HDF reaction

As described in our proposed mechanism, we believed that the reaction proceeds through a perfluoroaryl radical. Trapping the radical with a radical trapping reagent would be informative. For that we performed an experiment with pentafluoropyridine as the perfluoroarenes and TEMPO ((2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl) as the trapping reagent. The reaction was carried out under the standard conditions as shown in the Scheme 2.7. Unfortunately, no reaction was observed suggesting that the TEMPO prevents electron transfer to the perfluoroarene, which prevents fragmentation.



Scheme 2.7 Failed radical trapping experiment with TEMPO

In an additional attempt to confirm the generation of a perfluoroaryl radical, we attempted to trap it with an alkene. Radical addition to alkenes are well known.[54] Such transformations have relatively small energy barriers preventing addition to π-bonds, and are also exothermic and have fast kinetics (i.e., unactivated alkenes, such as hexene, are generally attacked by aryl radicals with a rate constant of k ~10^7 $M^{-1}S^{-1}$).[54a] After an unsuccessful attempt with TEMPO, we carried out a reaction with pentafluoropyridine as the perfluoroarenes and styrene as the alkene partner to trap the perfluoroaryl radical. Fortunately, the reaction took place and after quenching the reaction, the desired product (molecular ion of *m/z* 255) was detected by GC-MS which supported the formation of a perfluoroaryl radical as an intermediate in the photo-HDF reaction.



Scheme 2.8 Trapping of perfluoroaryl radical with styrene

2.2 Summary of the hydrodefluorination reaction

In summary, during this project we developed a novel photocatalytic HDF as a viable method to access polyfluorinated arenes using cheap and abundant perfluoroarenes as starting materials. This can be considered as a viable alternative to current HDF strategies in which we demonstrated the importance of avoiding the metal-F bond for catalytic turnover. A photocatalyst; *fac*-Ir(ppy)$_3$ was used as the electron transfer reagent to generate the perfluoroaryl radical *in situ*. Coordinatively saturated, 18 electron *fac*-Ir(ppy)$_3$ avoided the formation of strong metal–fluoride bonds, allowing a previously unprecedented catalyst TON for the HDF reaction. One desirable outcome is the use of safer and less expensive amine reductant than the traditional aluminum and silyl hydrides. Importantly, we have demonstrated that with a single catalyst we can perform mono-HDF, di-HDF and even tri-HDF on a number of different types of arenes simply by manipulating the equivalents of the amine reductant added in the reaction. To date, the work done by our group and others has increased the substrate scope to more than 250 substrates and still counting, which displays the versatility of the method. The transformation gives facile access to polyfluorinated aromatic rings, a task for which selective fluorination is poorly suited. Finally, we have demonstrated that the chemistry is amenable to flow methods, suggesting that it could be used to make sizable quantities of polyfluorinated arenes in a convenient, safe, and cost effective manner. We believe this method has great potential to help in a number of research areas where the partially fluorinated arenes are urgently needed.

2.3 Experimental section

General Experimental

All reagents were obtained from commercial suppliers (Sigma-Aldrich, Oakwood chemicals, Alfa Aesar, Matrix Scientific) and used without further purification, unless otherwise noted. Acetonitrile (MeCN) was dried over molecular sieves. *N*,*N*-diisopropylethylamine (*i*Pr_2NEt) was purchased from Sigma-Aldrich. Photocatalyst *tris*(2-phenylpyridinato-C^2, *N*)iridium(III)($Ir(ppy)_3$), 99%(purity), ($Ir(ppy)_3$) was obtained from Sigma-Aldrich. Methyl 2,3,4,5,6-pentafluorobenzoate (**2.7i'**), *tert*-butyl 2,3,4,5,6-pentafluorobenzoate (**2.7g'**), 2-(perfluorophenyl)benzo[*d*]oxazole (**2.7m'**), 4,4'-((perfluoro-1,4-phenylene)bis(oxy))bis(bromobenzene) (**2.7o'**), 4-amino-2,3,5,6-tetrafluorobenzonitrile (**2.7l'**), 1,2,4,5-tetrafluoro-3-phenoxy-6-(trifluoromethyl)benzene (**2.7e'**), *O*-ethyl *S*-(perfluorophenyl) carbonothioate (**2.7p'**), *N*-(perfluoropyridin-4-yl)acetamide (**2.7u'**), methyl 4-amino-2,3,5,6-tetrafluorobenzoate (**2.7h'**), *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide (**2.7f'**), 1,2,3,4-tetrafluorodibenzo[*b*,*e*][1,4]dioxine (**2.7r'**) and 4,5,6,7-tetrafluoro-2-phenylbenzofuran (**2.7s'**) were synthesized according to literature procedures. Photocatalysts ruthenium-tris(2,2′-bipyridyl) dichloride [$Ru(bpy)_3Cl_2$] and tris(bipyrimidine)ruthenium(II) dichloride [$Ru(bpm)_3Cl_2$] were synthesized according to literature procedures (McFarland, S. A.; Lee, F. S.; Cheng, K. A. W. Y.; Cozens, F. L.; Schepp, N. P. *J. Am. Chem. Soc.* **2005**, *127*, 7065 and Ross, H. B.; Boldaji, M.; Rillema, D. P.; Blanton, C. B.; White, R. P. *Inorg. Chem.* **1989**, *28*, 1013). Reactions were monitored by ^{19}F and GC-MS (Shimadzu, QP 2010S, equipped with auto sampler). NMR spectra were obtained on 400 MHz Bruker Avance III spectrometer and 400 MHz Unity Inova spectrometer. ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^1H, ^{13}C) and ^{19}F NMR shifts are reported using TFA as a standard. IR spectra were recorded on a Perkin Elmer 2000 FT-IR. Melting points were determined on a Mel-Temp apparatus and are uncorrected. GC analyses were carried out using an Agilent 6850 Series GC

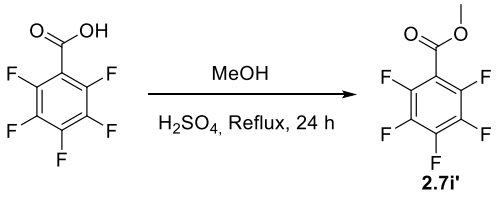
system. Isolations were carried out using a Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica (4 g, 12 g, or 24 g) with product detection at 254 and 280 nm. Some isolations were performed using Sorbent Technology Silica Prep TLC plates w/UV254, glass backed, 1000 µm, 20 x 20 cm and were visualized with ultraviolet light. Substrate synthesis reactions were monitored by thin layer chromatography (TLC) obtained from Sorbent Technology; Silica XHL TLC plates, w/UV254, glass backed, 250 µm, and were visualized with ultraviolet light or potassium permanganate.

Photocatalytic reactions were set up in a light bath which is described below. Strips of blue LEDs, (18 LEDs/ft) were purchased from Solid Apollo and were wrapped around the walls of a glass crystallization dish and secured with masking tape and then wrapped with aluminum foil. A lid which rested on the top was fashioned from cardboard and holes were made such that reaction tubes (12 × 75 mm cultural borosilicate tube) were held firmly in the cardboard lid which was placed on the top of the bath. Water was added to the bath such that the tubes were submerged in the water, which was maintained at 45 ^{o}C with the aid of a sand bath connected to a thermostat.

Experimental setup for the HDF reaction

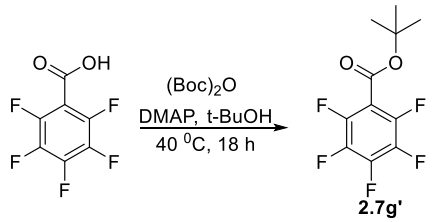
Synthesis of substrates

Synthesis of methyl 2,3,4,5,6-pentafluorobenzoate (2.7i')



2.7i' was prepared using an unoptimized procedure. In a 100 mL of round-bottomed flask, pentafluorobenzoic acid (Oakwood Chemicals) (2.0 g, 9.4 mmol) and MeOH (32.0 g, 1000 mmol) were added followed by conc. H_2SO_4 (1.8 g, 18.8 mmol). The mixture was refluxed overnight and monitored by TLC (Hexane: EtOAc 90:10). After the completion of reaction it was concentrated *in vacuo*, dissolved in CH_2Cl_2 (25 mL) and added to saturated Na_2CO_3 to neutralize the reaction mixture. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL) and the combined organic layers were washed with brine (20 mL), water (20 mL) and dried (Na_2SO_4), filtered and concentrated *in vacuo* to leave methyl 2,3,4,5,6-pentafluorobenzoate in 75% yield (1.6 g, 7.2 mmol) as a colorless liquid. The NMR spectra of the product matched those reported in the literature (Lv, H.; Cai, Y.-B.; Zhang, J.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 3203). The product was used without further purification.

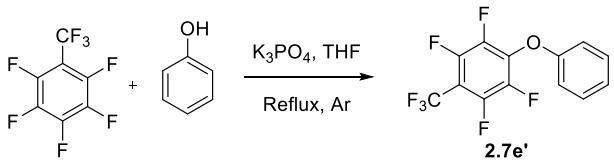
Synthesis of *tert*-butyl 2,3,4,5,6-pentafluorobenzoate (2.7g')



2.7g' was prepared by a modified literature procedure (Brown, A. D.; Rawson, D. J.; Storer, R. I.; Swain, N. A.; PCT Int. Appl., 20120078692). In a 100 mL of round-bottomed flask,

pentafluorobenzoic acid (Oakwood Chemicals) (2.0 g, 9.4 mmol) and dimethylaminopyridine (116 mg, 0.95 mmol) were dissolved in *tert*-butanol (30 mL). di-*tert*-butyldicarbonate (4.1 g, 18.9 mmol) was added and the reaction heated to 40 °C for 18 hours. The reaction was quenched with 1M HCl (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with saturated Na_2CO_3 (3 x 20 mL) , followed by brine (1 x 15 mL) then concentrated *in vacuo* to yield *tert*-butyl 2,3,4,5,6-pentafluorobenzoate as a colorless liquid in 80% yield (2.0 g, 7.5 mmol), that matches with NMR spectra of product reported in the literature (Brown, A. D.; Rawson, D. J.; Storer, R. I.; Swain, N. A.; PCT Int. Appl., 2012007869). The product was used without further purification.

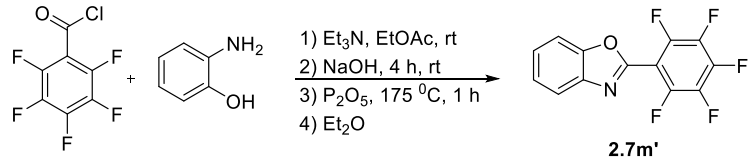
Synthesis of 1,2,4,5-tetrafluoro-3-phenoxy-6-(trifluoromethyl)benzene (**2.7e'**)



2.7e'

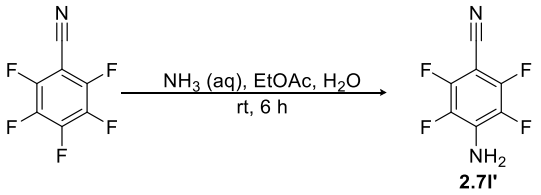
2.7e' was prepared by a modified literature procedure (Zhang, J.; Wu, J.; Xiong, Y.; Cao, S. *Chem. Commun.* **2012**, *48*, 8553). In a 100 mL of round-bottomed flask octafluorotoluene (Oakwood Chemicals) (2.0 g, 8.47 mmol), phenol (956 mg, 10.2 mmol) were dissolved in THF (50 mL) . K_3PO_4 (3.6 g, 16.94 mmol) was added and the reaction mixture was refluxed for 8 hours under argon atmosphere and monitored by TLC. The resulting suspension was filtered and the filtrate was diluted with CH_2Cl_2 (25 mL), washed successively with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave the crude product. The resultant crude residue was purified by automated flash chromatography using hexane to give the product 1,2,4,5-tetrafluoro-3-phenoxy-6-(trifluoromethyl)benzene as colorless crystals in 50% yield (1.3 g, 4.2 mmol). The NMR spectra of product matched those reported in the literature (Zhang, J.; Wu, J.; Xiong, Y.; Cao, S. *Chem. Commun.* **2012**, *48*, 8553).

Synthesis of 2-(perfluorophenyl)benzo[*d*]oxazole (**2.7m'**)



2.7m' was prepared by literature procedure (Balazs, Y. S.; Saltsman, I.; Mahammed, A.; Tkachenko, E.; Golubkov, G.; Levine, J.; Gross, Z. *Magn. Reson. Chem.* **2004**, *42*, 624). Pentafluorbenzoic acid (3.0 g, 14.1 mmol) and DMF was slowly added to $SOCl_2$ (23.0 g, 200 mmol). The mixture was refluxed overnight under an Ar atmosphere. 2-(perfluorophenyl)benzo[*d*]oxazole was prepared by following literature procedure (Tanaka, K.; Deguchi, M.; Yamaguchi, S.; Yamada, K.; Iwata, S. *J. Heterocycl. Chem.* **2001**, *38*, 131). Triethylamine (1.7 g, 16.9 mmol) was added dropwise to a solution of 2-aminophenol (1.4 g, 12.7 mmol) and pentafluorobenzoyl chloride previously prepared (*vide supra*) in ethyl acetate (50 mL). Mixture was refluxed overnight and then aq NaOH (1M, 30 mL) was added and stirred for 3 hours at room temperature. The resulting mixture was extracted with EtOAc (5 × 20 mL) and washed with H_2O (25 mL) and brine (25 mL). Organic layer was dried over anhydrous $MgSO_4$ to yield 4 g of intermediate. P_2O_5 (4.0 g, 28 mmol) was added to the intermediate and then heated at 175 ^oC for 1 hour. After the mixture was cooled to room temperature ice water (50 mL) was added and mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with aq NaOH (0.25 M, 50 mL), followed by water, brine and dried over anhydrous $MgSO_4$ and then concentrated *in vacuo* to leave the crude product. The resultant crude residue was purified by automated flash chromatography (hexane : EtOAc 90:10) to give the product 2-(perfluorophenyl)benzo[*d*]oxazole as white solid in 35% yield (1.2 g, 4.2 mmol). The NMR spectra of product matched those reported in the literature (Tanaka, K.; Deguchi, M.; Yamaguchi, S.; Yamada, K.; Iwata, S. *J. Heterocycl. Chem.* **2001**, *38*, 131).

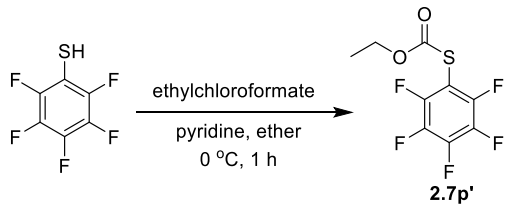
Synthesis of 4-amino-2,3,5,6-tetrafluorobenzonitrile (**2.7l'**)



2.7l'

2.7l' was prepared according to literature procedures (Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598). To a solution of 2,3,4,5,6-pentafluorobenzonitrile (2 g, 10.4 mmol) in EtOAc (10 mL) was added a solution of aq. NH_3 (0.9 g,14.5 mmol, 28% w/w) and water (2 mL) dropwise and the reaction flask was stirred at room temperature for 6 hours. The reaction was monitored by TLC (hexane: EtOAc 90:10). Upon completion, water (4 mL) was added and stirred for 1 hour, and the resultant mixture was extracted with EtOAc (3 x 20 mL), dried over anhydrous sodium sulfate and then concentrated *in vacuo* to afford 2,3,5,6-tetrafluorobenzonitrile in 60 % yield (1.2 g, 6.3 mmol) as light yellow solid. The NMR spectra of product matched those reported in the literature (Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598).

Synthesis of S-2o *O-ethyl S*-(2,3,5,6-tetrafluorophenyl) carbonothioate (**2.7p'**)

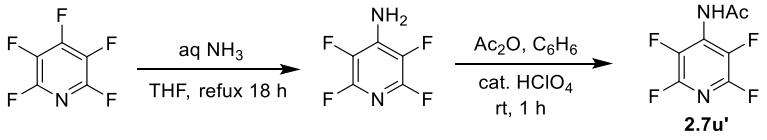


2.7p'

2.7p' was synthesized according to a literature procedure (Castro, E. A.; Aliaga, M.; Campodónico, P. R.; Cepeda, M.; Contreras, R.; Santos, J. G. *J. Org. Chem.* **2009**, *74*, 9173). In a 100 mL round-bottomed flask, pentafluorothiophenol (0.66 mL, 5 mmol), pyridine (0.6 mL, 7.5 mmol) and ether (17 mL) were added. The reaction mixture was stirred at 0 °C under Ar for 2 min

and then ethylchloroformate (0.478 mL, 5mmol) was added to the reaction mixture dropwise and stirring was continued for 2 h. Reaction mixture was washed with cold HCl (1 x 20 mL 1M), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using Hexane:DCM (0 % DCM for 10 cv and ramped slowly to 30 % DCM for 10-30 cv and then held at 35% DCM 30-35 cv) on a 24 g silica column)) to afford *O*-ethyl *S*-perfluorophenyl carbonothioate in 29% yield (0.4 g, 1.47 mmol) as colorless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.33 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -130.77 (dt, *J* = 21.7, 5.7 Hz, 2F), -149.18 (tt, *J* = 20.9, 3.9 Hz, 1F), -160.67 (tt, *J* = 21.1, 4.9 Hz, 2F).

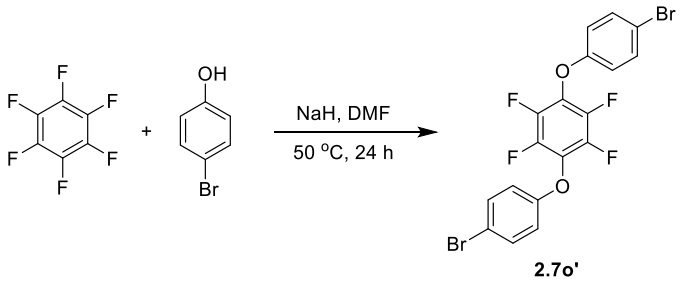
Synthesis of N-(perfluoropyridin-4-yl)acetamide (**2.7u'**)



2.7u' was synthesized by following literature procedures (Sekhri, L. *Asian J. Chem.* **2005**, *17*, 1747 and Laev, S. S.; Evtefeev, V. U.; Shteingarts, V. D. *J. Fluorine Chem.* **2001**, *110*, 43). In a 50 mL reaction flask, pentafluoropyridine (0.3 mL , 2.96 mmol), conc. ammonia (1 mL), and THF (5 mL) were added. The reaction mixture was heated to reflux for 18 h. The flask was cooled to room temperature and THF was removed *in vacuo*. To the residue, water (10 mL) was added and aqueous portion was extracted with dichloromethane (3 x 10 mL). The combined DCM portion was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give 2,3,5,6-tetrafluoropyridin-4-amine as a yellow solid (0.544 g, 3.26 mmol) which was used without further purification in the acetylation step. In a 50 mL reaction flask, 2,3,5,6-tetrafluoropyridin-4-amine (0.544 g, 3.26 mmol), acetic anhydride (0.39 mL, 4.1 mmol), conc. $HClO_4$ (17μL, 0.28 mmol) and benzene (5 mL) were added and stirred at room temperature for 1h. The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined ethyl

acetate portion was washed with water (1 x 10 mL), 1 M HCl (1 x 10 mL) and brine (1 x 10 mL). The ethyl acetate portion was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using hexane with 1% acetic acid:ethyl acetate (0 – 50% EtOAc for 30 cv and ramped to 100 % EtOAc for 30-40 cv) on a 12 g silica column) to afford *N*-(perfluoropyridin-4-yl)acetamide in yield 33% (0.2 g, 1.47 mmol) as a white solid. The NMR spectra of product matched those reported in the literature.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (s, 1H), 2.30 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -89.87 (dq, *J* = 29.2, 14.0 Hz, 2F), -146.03 – -146.27 (m, 2F).

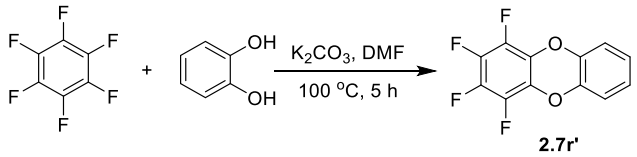
1,4-bis(4-bromophenoxy)benzene (**2.7o'**)



2.7o'

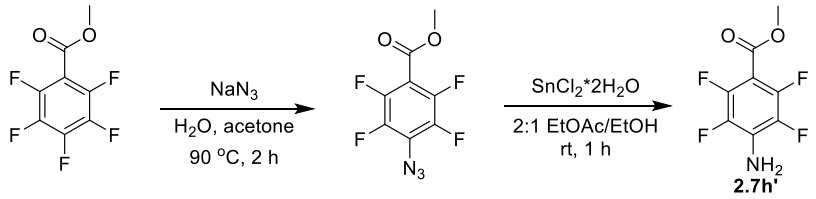
2.7o' was synthesized by following literature procedure (Ponce Gonzalez, J.; Edgar, M.; Elsegood, M. R. J.; Weaver, G. W. *Organic & Biomolecular Chemistry* **2011**, *9*, 2294). In a three necked 100 mL reaction flask, hexafluorobenzene (1.2 mL, 10.7 mmol), sodium hydride (428 mg, 10.7 mmol) and DMF (10 mL) were added. The suspension was stirred at 0 °C for 10 min and then 4- bromophenol (0.9 g, 5.35 mmol) was added dropwise to the suspension. The resulting mixture was stirred at 50 °C for 24 h. The reaction mixture was cooled to room temperature. The cooled mixture was diluted with water (50 mL) and extracted with ether (3 x 40 mL). The combined ether portion was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using 100% hexanes to afford 1g in 16% yield (0.425 g, 0.86 mmol) as a colorless solid which was matched with literature.[10] ^{19}F NMR (376 MHz, Chloroform-*d*) δ -154.18 (s, 4F).

1,2,3,4-tetrafluorodibenzo[b,e][1,4]dioxine (**2.7r'**)



2.7r' was synthesized by following a literature procedure (Li, S.; Fa, S.-X.; Wang, Q.-Q.; Wang, D.-X.; Wang, M.-X. *J. Org. Chem.* **2012**, *77*, 1860). In a 100 mL reaction flask, hexafluorobenzene (1.15 mL, 10.0 mmol), potassium carbonate (1.38 g, 10.0 mmol), catechol (1.101 g, 10 mmol) and DMF (25 mL) were added. The reaction mixture was stirred at 100 °C for 5 h. The reaction mixture was cooled to room temperature. The cooled mixture was treated with 10 % HCl to obtain pH 4 and extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate was washed with water (3 x 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford **2.7r'** in 21% yield (0.528 g, 2.06 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 – 6.93 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -162.99 (td, *J* = 16.7, 15.8, 10.0 Hz, 2F), -165.73 (td, *J* = 16.8, 15.8, 10.1 Hz, 2F).

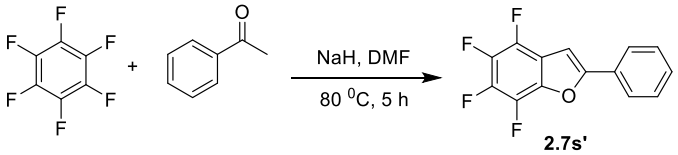
Methyl 4-amino-2,3,5,6-tetrafluorobenzoate (**2.7h'**)



2.7h' was synthesized by following literature procedures (Norberg, O.; Deng, L.; Yan, M.; Ramström, O. *Bioconjugate Chem.* **2009**, *20*, 2364 and Gee, K. R.; Keana, J. F. W. *Synth. Commun.* **1993**, *23*, 357). In a 50 mL reaction flask, methyl-2,3,4,5,6-pentafluorobenzoate (0.5 g, 2.2 mmol), sodium azide (186 mg, 2.86 mmol), acetone/ water (10 mL 2:1 v/v) were added. The

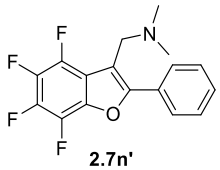
reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was cooled to room temperature and then diluted with water (60 mL). The reaction mixture was extracted with ether (3 x 20 mL). The combined ether portions were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford methyl 4-azido-2,3,5,6-tetrafluorobenzoate (0.451 g, 1.8 mmol) as a brown solid which matched with literature.[12] In a 50 mL round-bottomed flask, methyl 4-azido-2,3,5,6-tetrafluorobenzoate (0.426 g, 1.7 mmol), $SnCl_2*2H_2O$ (0.579 mg, 2.56 mmol), ethyl acetate / ethanol (15 mL 2:1 v/v) were added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and treated with sat. $NaHCO_3$ (20 mL). The aqueous mixture was extracted with dichloromethane (3 x 15 mL) and filtered through celite to obtain methyl-4-amino-2,3,5,6-tetrafluorobenzoate in crude yield 89% (0.438 g, 1.96 mmol) as a brownish yellow solid. The NMR spectra of product matched those reported in the literature (Gee, K. R.; Keana, J. F. W. *Synth. Commun.* **1993**, *23*, 357). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.89 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -141.03 – -141.22 (m, 2F), -162.62 – -162.76 (m, 2F).

4,5,6,7-tetrafluoro-2-phenylbenzofuran (**2.7s'**)



2.7s' was synthesized by the following literature procedure (Inukai, Y.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2657). To a suspension of hexafluorobenzene (1.15 mL, 10 mmol), NaH (0.24 g, 20 mmol) and DMF (10 mL), was added a solution of acetophenone (1.16 mL, 10 mmol) dropwise. The reaction mixture was stirred at 80 °C for 5 h. The reaction mixture was cooled to room temperature and poured into ether (100 mL). The reaction mixture was washed water (3 x 20 mL). The combined ether portions were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash

chromatography using hexane:DCM (0 – 10% DCM for 15 cv and ramped to 100 % EtOAc for 15-25 cv) on 80 g silica column) to afford 4,5,6,7-tetrafluoro-2-phenylbenzofuran in yield 15% (0.4 g, 1.5 mmol) as a white solid which matched with the literature (Inukai, Y.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2657). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dt, *J* = 6.1, 1.3 Hz, 2H), 7.50 – 7.38 (m, 3H), 7.10 (d, *J* = 2.3 Hz, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -147.99 – -148.20 (m, 1F), -161.81 – -162.13 (m, 2F), -164.53 (ddd, *J* = 21.2, 15.1, 6.5 Hz, 1F).

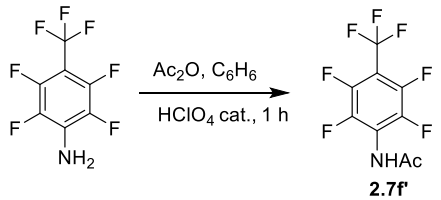


2.7n'

(4,5,6,7-tetrafluoro-2-phenylbenzofuran-3-yl)-N,N-dimethylmethanamine (**2.7n'**)

2.7n' was obtained as a by-product in the synthesis of **1u** in 8% yield (0.28 g, 0.86 mmol) (*vide supra*) as a yellow waxy solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 8.00 (m, 2H), 7.49 (ddd, *J* = 17.5, 13.0, 11.6 Hz, 3H), 3.68 (s, 2H), 2.36 (s, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -149.31 (dd, *J* = 20.8, 16.1 Hz, 1F), -162.22 (t, *J* = 19.7 Hz, 1F), -162.52 – -162.78 (m, 1F), -164.84 (t, *J* = 20.3 Hz, 1F). GC/MS (*m/z*, relative intensity) 323 (M+, 40), 308 (80), 279 (100), 251 (36), 201 (39).

***N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide** (**2.7f'**)

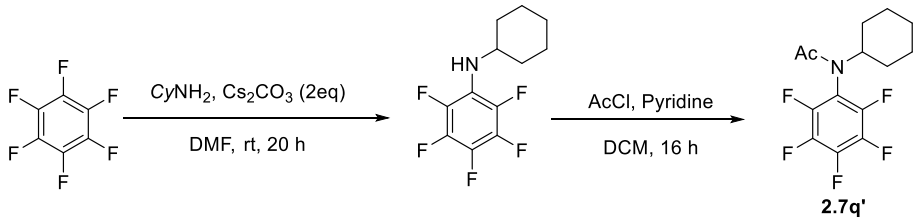


2.7f'

2.7f' was synthesized according to the literature procedure (Laev, S. S.; Evtefeev, V. U.; Shteingarts, V. D. *J. Fluorine Chem.* **2001**, *110*, 43). Starting amine was synthesized according

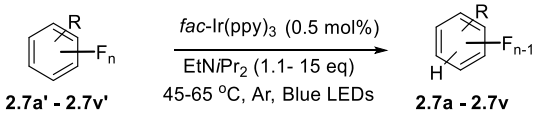
to literature procedure (Sekhri, L. *Asian J. Chem.* **2005**, *17*, 1747). In a 25 mL reaction flask, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzenamine (0.5 g, 2.15 mmol), acetic anhydride (0.29 mL, 3.06 mmol), conc. $HClO_4$ (10µL) and benzene (5 mL) were added and stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate portion was washed with water (1 x 10 mL), 1 M HCl (1 x 10 mL) and brine (1 x 10 mL). The ethyl acetate portion was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 – 40% EtOAc for 5 cv and ramped slowly to 100 % EtOAc for 5-45 cv and then held at 100% EtOAc 45-48 cv) on a 24 g silica column) to afford *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide in yield 76% (0.45 g, 1.63 mmol) as a white solid. The NMR spectra of product matched those reported in the literature.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.86 (s, 1H), 2.27 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -56.53 (t, *J* = 21.7 Hz, 3F), -140.48 – -141.37 (m, 2F), -143.13 – -143.91 (m, 2F).

***N*-cyclohexyl-N-(perfluorophenyl)acetamide (2.7q')**



N-cyclohexyl-2,3,4,5,6-pentafluoroaniline was synthesized following the literature procedure (Lefèvre, G.; Franc, G.; Adamo, C.; Jutand, A.; Ciofini, I. *Organometallics* **2012**, *31*, 914). 1k was synthesized by the acylation of above amine. To an ice cold solution of *N*-cyclohexyl-2,3,4,5,6-pentafluoroaniline (1.9 g, 7.5 mmol), DCM (30 mL) and pyridine (1.2 mL, 15 mmol), acetyl chloride (1.0 mL, 15 mmol) was added dropwise. Reaction was stirred at room temperature for 16 hours. Reaction was quenched by adding sat. NH_4Cl (25 mL) and aq phase was extracted with DCM (20 x 5). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash

chromatography using hexane:EtOAc (0 – 50% EtOAc for 15 cv and ramped to 100 % EtOAc for 15-18 cv and then hold for 18-21) on a 80 g silica column to afford *N*-cyclohexyl-*N*-(perfluorophenyl)acetamide in yield 60% (86% purity) (1.35 g, 4.39 mmol) as a colorless solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.57 (tt, *J* = 12.2, 3.6 Hz, 1H), 1.95 – 1.67 (m, 7H), 1.37 (tdd, *J* = 16.6, 8.3, 3.4 Hz, 2H), 0.91 – 0.78 (m, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -141.86 (d, *J* = 18.3 Hz), -152.31 (t, *J* = 21.5 Hz), -160.90 – -161.13 (m). In ^{19}F NMR another set of 2:1:2 peaks with similar multiplicity was noticed which integrated to 14%. mp 58-60 °C.



2.7a' - 2.7v' **2.7a - 2.7v**

General procedure A for the photocatalytic hydrodefluorination reaction (reaction in culture tube)

A 12 x 75 mm borosilicate test tube fitted with rubber septum was charged *tris*(2-phenylpyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.5 mM, 1 mL in MeCN). Fluorinated starting material **2.7a' - 2.7v'** (1 equiv) and *i*Pr_2NEt **(**1.1-15 equiv) were added and the reaction was degassed at 0 °C to avoid evaporation of *i*Pr_2NEt and volatile starting materials *via* Ar bubbling for 5-10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (*vide supra*) and the lower portion of the tube was submerged under the water bath which was maintained at 45 °C (or 65 °C). The reaction was monitored by ^{19}F NMR and GC-MS. For ^{19}F NMR 0.3 mL of reaction mixture was diluted with 0.3 mL of $CDCl_3$ after the desired time period. After the complete consumption of starting material, the CH_3CN was removed *via* rotavap and the residue was treated with deionized water (2 mL) and extracted with EtOAc (5 x 1 mL). The combined organic portions were dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by normal phase chromatography.

General procedure B for the photocatalytic hydrodefluorination reaction (reaction NMR tube with C_6D_6 capillary)

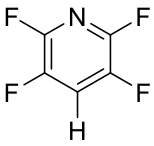
In an NMR tube capped with NMR septa (Ace glass, part no. 9096-25) was charged *tris*(2-phenylpyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.5 mM, 1 mL in MeCN). Fluorinated starting material **2.7a' - 2.7v'** (1 equiv) and *N*, *N*-diisopropylethylamine (1.1-15 equiv) were added and sealed glass capillary containing C_6D_6 was placed in NMR tube for locking purposes before degassing. Then the reaction was degassed at 0 °C to avoid evaporation of *N*, *N*-diisopropylethylamine and volatile starting materials *via* Ar bubbling for 5-10 min. The NMR tube was placed in a light bath (*vide supra*) and the lower portion of the tube was submerged under the water bath which was maintained at 45 °C (or 65 °C). The reaction was monitored by ^{19}F NMR. After the complete consumption of starting material, CH_3CN was removed *via* rotavap and the residue was treated with deionized water (2 mL) and extracted with EtOAc (5 x 1 mL). The combined organic portions were dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by normal phase chromatography.

General procedure C for the photocatalytic hydrodefluorination reaction (reaction NMR tube)

In an NMR tube capped with NMR septa (Ace glass, part no. 9096-25) was charged *tris*(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.5 mM, 1 mL in MeCN). Fluorinated starting material **2.7a' - 2.7v'** (1 equiv) and *N*, *N*-diisopropylethylamine **(**1.1-15 equiv) were added and the reaction was degassed at 0 °C to avoid evaporation of *N*, *N*-diisopropylethylamine and volatile starting materials *via* Ar bubbling for 5-10 min. The NMR tube was placed in a light bath (*vide supra*) and the lower portion of the tube was submerged under the water bath which was maintained at 45 °C (or 65 °C). The reaction was monitored by ^{19}F NMR. After the complete consumption of starting material, CH_3CN was removed *via* rotavap and the residue was treated

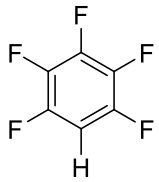
with deionized water (2 mL) and extracted with EtOAc (5 x 1 mL). The organic portions were combined and dried with anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified by normal phase chromatography. For ^{19}F NMR 0.3 mL of above reaction was diluted with 0.3 mL of $CDCl_3$.

Synthesis of 2.7a (2,3,5,6-tetrafluoropyridine)



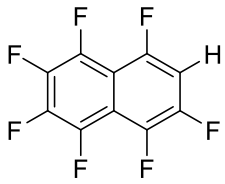
The general procedure **A** was followed using pentafluoropyridine (16.9 mg, 0.1 mmol, 1 equiv), *i*Pr_2NEt (28 mg mg, 0.22 mmol, 2.2 equiv) and 1.0 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7a** in 93% yield by ^{19}F NMR after adding trifluoroacetic acid (0.050 mmol, 3.8 µL). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -93.5 (br s, 2F), -141.4 – -141.7 (m, 2F). FT-IR cm^{-1}2983, 1696, 1472, 1396. GC/MS (*m/z*, relative intensity) 151 (M+, 100), 132 (10), 120 (17), 106 (23), 82 (50).

Synthesis of 2.7b (1,2,3,4,5-pentafluorobenzene)



The general procedure **A** was followed using hexafluorobenzene (18.6 mg, 0.1 mmol, 1 equiv), *i*Pr_2NEt (43 mg, 0.33 mmol, 3.3 equiv) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7b** in 90% yield by ^{19}F NMR after adding trifluoroacetic acid (0.033 mmol, 2.5 µL). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -140.2 (dt, *J* = 20.1, 9.3 Hz, 2F), -155.8 (t, *J* = 19.6 Hz, 1F), -163.8 (ddt, *J* = 25.9, 12.7, 6.9 Hz, 2F) which matched with the literature value (Jana, A.; Roesky, H. W.; Schulzke, C.; Samuel, P. P. *Organometallics* **2010**, *29*, 4837). FT-IR cm^{-1}3004, 2985, 1669, 1576.

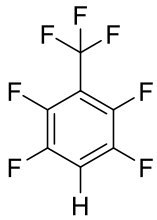
Synthesis of 2.7c (1,2,3,4,5,6,8-heptafluoronaphthalene)



The general procedure **B** was followed at 65 ºC in an NMR tube using perfluoronaphthalene (13.6 mg, 0.05 mmol, 1 equiv), *i*Pr_2NEt (22 mg, 0.17 mmol, 3.3 equiv) and 0.5 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was

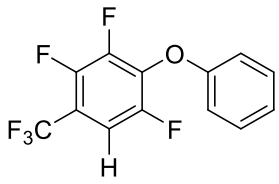
used to afford **2.7c** in 55% yield (at 57% conversion) by ^{19}F NMR after adding trifluoroacetic acid (0.025 mmol, 1.9 µL). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -118.8 – -119.1 (m, 1F), -136.5 – -136.6 (m, 1F), -147.2 (dt, *J* = 65.4, 16.3 Hz, 1F), -148.9 – -149.2 (m, 1F), -152.2 – -152.6 (m, 1F), -156.2 (t, *J* = 17.8 Hz, 1F), -158.8 – -159.0 (m, 1F) which matched with the literature value (Bolton, R.; Sandall, J. P. B. *Journal of the Chemical Society, Perkin Transactions 2* **1978**, 746). FT-IR cm^{-1} 3003, 2985, 1652, 1482.

Synthesis of 2.7d (1,2,4,5-tetrafluoro-3-(trifluoromethyl)benzene)



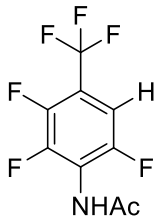
The general procedure **B** was followed using 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)benzene (24.0 mg, 0.1 mmol, 1 equiv), *i*Pr_2NEt (14 mg, 0.11 mmol, 1.1 equiv) and 1.0 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7d** in 95% yield by ^{19}F NMR after adding trifluoroacetic acid (0.050 mmol, 3.8 µL). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -57.4 (t, *J* = 22.1 Hz, 3F), -137.8 – -137.9 (m, 2F), -142.0 – -142.4 (m, 2F). FT-IR cm^{-1} 3201, 1653. GC/MS (*m/z*, relative intensity) 218 (M+, 40), 200 (70), 181 (69), 150 (60), 86 (100).

Synthesis of 2.7e (1,3,4-trifluoro-2-phenoxy-5-(trifluoromethyl)benzene)



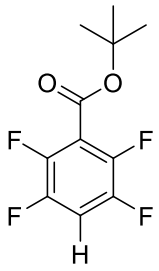
The general procedure **B** was followed using 4-amino-2,3,5,6-tetrafluorobenzonitrile (31.0 mg, 0.1 mmol), *i*Pr_2NEt (14 mg, 0.11 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7e** in 90% yield by ^{19}F NMR after adding trifluoroacetic acid (0.025 mmol, 1.9 µL). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.9 (d, *J* = 13.0 Hz, 3H), -130.9 (t, *J* = 11.4 Hz, 1F), -142.9 – -143.2 (m, 1F), -147.9 (d, *J* = 19.2 Hz, 1F). FT-IR cm^{-1} 2980, 1653, 1591, 1511, 1385, 1491, 1233. GC/MS (*m/z*, relative intensity) 292 (M+, 100), 273 (8), 264 (7), 74 (100), 51 (48).

Synthesis of 2.7f (*N*-(2,3,6-trifluoro-4-(trifluoromethyl)phenyl)acetamide)



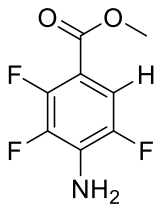
The general procedure **A** was followed using *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide (27 mg, 0.10 mmol), *i*Pr_2NEt (14 mg, 0.11 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7f** in 80% isolated yield (21mg, 0.080 mmol) as a yellow solid. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 – 40% EtOAc for 5 cv and ramped slowly to 100 % EtOAc for 5-45 cv and then held at 100% EtOAc 45-48 cv) on a 24 g silica column). ^{19}F NMR (376 MHz, Acetone-d_6) δ -61.9 (d, J = 13.0 Hz, 3F), -121.5 – -121.8 (m, 1F), -137.5 (d, J = 19.4 Hz, 1F), -145.5 – -145.7 (m, 1F). ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.30 (s, 1H), 7.52 (ddd, J = 8.7, 5.8, 2.2 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 167.6, 152.6 (dt, J = 248.1, 3.8 Hz), 147.9 – 145.0 (m), 146.6 – 143.6 (m), 121.8 (d, J = 277.8 Hz), 123.8 – 119.9 (m), 116.1 – 115.5 (m), 108.6 (dt, J = 27.2, 4.7 Hz), 21.8. FT-IR cm^{-1} 3441, 3022, 2978, 1644, 1521. GC/MS (*m/z*, relative intensity) 257 (M+, 2), 215 (60), 196 (20), 165 (11). mp 162-166 °C.

Synthesis of 2.7g (*tert*-butyl 2,3,5,6-tetrafluorobenzoate)



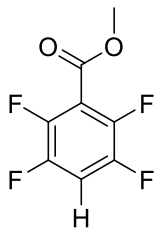
The general procedure B was followed at 45 °C using *tert*-butyl 2,3,4,5,6-pentafluorobenzoate (27 mg, 0.10 mmol), *i*Pr_2NEt (14 mg, 0.11 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7g** in 90% yield by ^{19}F NMR after adding trifluoroacetic acid (0.025 mmol, 1.9 µL). ^{19}F NMR (376 MHz, Benzene-d_6) δ -140.2 – -140.3 (m, 2F), -143.7 – -143.9 (m, 2F). FT-IR cm^{-1} 3045, 2986, 1730, 1600, 1551, 1437, 1267. Calculated HRMS(ESI) for ($C_{11}H_{10}F_4O_2$ (M+NH_4)$^+$ is 268.0961 observed 268.1016.

Synthesis of 2.7h (methyl 4-amino-2,3,5-trifluorobenzoate)



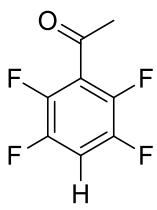
The general procedure A was followed using methyl 4-amino-2,3,5,6-tetrafluorobenzoate (44 mg, 0.20 mmol), *i*Pr_2NEt (85 mg, 0.66 mmol) and 2 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7h** in 99% isolated yield (41 mg, 0.20 mmol) as a white solid. The crude material was purified by flash chromatography using hexane : ethyl acetate (0-10 % EtOAc for 25 cv and ramped to 100 % EtOAc for 10-52 cv and then held at 100% EtOAc 52-57 cv) on 12 g silica column). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -138.4 (q, *J* = 10.9 Hz, 1F), -139.2 (ddd, *J* = 19.2, 12.8, 5.8 Hz, 1F), -156.5 (ddd, *J* = 19.7, 10.1, 2.2 Hz, 1F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (ddd, *J* = 11.2, 5.8, 2.3 Hz, 1H), 4.28 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.2 – 163.7 (m), 149.7 (dd, *J* = 11.7, 2.6 Hz), 144.9 (dd, *J* = 6.0, 2.4 Hz), 139.9 (ddd, *J* = 241.2, 16.9, 7.2 Hz), 147.7 – 129.6 (m), 112.3 (ddd, *J* = 21.8, 2.7, 1.2 Hz), 106.5 (dd, *J* = 8.6, 7.8 Hz), 52.5. FT-IR cm^{-1} 3403, 3050, 2984, 1732, 1551. GC/MS (*m/z*, relative intensity) 205 (M+, 46), 174 (100), 146 (33). mp 107-108 °C.

Synthesis of 2.7i (methyl 2,3,5,6-tetrafluorobenzoate)



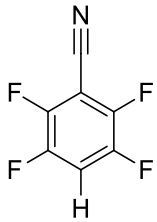
The general procedure B was followed using methyl 2,3,4,5,6-pentafluorobenzoate (23 mg, 0.10 mmol, 1.0 equiv), *i*Pr_2NEt (14 mg, 0.11 mmol, 1.1 equiv) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7i** in 75% yield by ^{19}F NMR after adding trifluoroacetic acid (0.025 mmol, 1.9 µL). ^{19}F NMR (376 MHz, Benzene-d_6) δ -139.8 – -140.5 (m, 2F), -142.2 – -142.4 (m, 2F). FT-IR cm^{-1} 3018, 2966, 1733, 1495, 1268. GC/MS (*m/z*, relative intensity) 151 (M+, 100), 132 (10), 120 (17), 106 (23), 82 (50).

Synthesis of 2.7j (1-(2,3,5,6-tetrafluorophenyl)ethan-1-one)



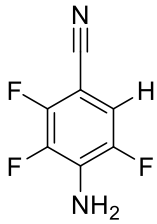
The general procedure A was followed using 1-(2,3,5,6-tetrafluorophenyl)ethanone (21 mg, 0.10 mmol, 1 equiv), *i*Pr_2NEt (19 mg, 0.15 mmol, 1.5 equiv) and 1.0 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7j** in 85% yield by ^{19}F NMR after adding trifluoroacetic acid (0.050 mmol, 3.8 µL). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.4 – -139.5 (m, 2F), -143.8 (tt, *J* = 12.9, 7.8 Hz, 2F). FT-IR cm^{-1} 2983, 1690, 1498. GC/MS (*m/z*, relative intensity) 192 (M+, 40), 177 (100), 149 (57), 99 (40).

Synthesis of 2.7k (2,3,5,6-tetrafluorobenzonitrile)



The general procedure A was followed using 2,3,4,5,6-pentafluorobenzonitrile (19 mg, 0.10 mmol), *i*Pr_2NEt (14 mg, 0.11 mmol) and 1.0 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.7k** in 88% yield by ^{19}F NMR after adding trifluoroacetic acid (0.050 mmol, 3.8 µL). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -135.4 – -135.6 (m, 2F), -138.4 (tdd, *J* = 15.6, 10.1, 6.0 Hz, 2F) which matched with the literature value (Lv, H.; Cai, Y.-B.; Zhang, J.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 3203). FT-IR cm^{-1} 2243, 1585, 1690, 1492. GC/MS (*m/z*, relative intensity) 175 (M+, 100), 144 (8), 124 (7), 106 (30).

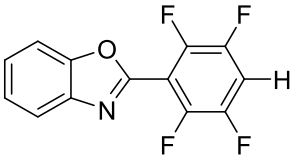
Synthesis of 2.7l (4-amino-2,3,5-trifluorobenzonitrile)



The general procedure A was followed using 4-amino-2,3,5,6-tetrafluorobenzonitrile (19 mg, 0.10 mmol), *i*Pr_2NEt (14 mg, 0.11 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % for 1 cv, slowly ramped to 12% EtOAc for 1-12 cv, to 20% EtOAc for 12-26 cv, to 25% EtOAc for 26-32 cv then ramped to 100 % EtOAc for 32-34 cv, then held at 100% EtOAc 34-40 cv), on a 24 g silica column) to afford **2.7l** in 82% isolated yield (14 mg, 0.082 mmol) as a light brown solid.

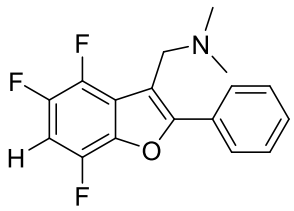
^{19}F NMR (376 MHz, Chloroform-*d*) δ -135.3 (ddd, *J* = 19.7, 11.3, 5.0 Hz, 1F), -135.6 – -135.7 (m, 1F), -154.1 (ddd, *J* = 19.3, 12.2, 1.9 Hz, 1F). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.37 (ddd, *J* = 10.6, 5.4, 2.2 Hz, 1H), 6.19 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.9 (ddd, *J* = 256.1, 12.4, 3.4 Hz), 146.6 (dd, *J* = 242.1, 4.7 Hz), 146.5 (dd, *J* = 238.5, 0.7 Hz), 139.4 (ddd, *J* = 243.7, 14.9, 7.8 Hz), 131.9 (ddd, *J* = 17.3, 12.3, 3.6 Hz), 113.8 (ddd, *J* = 23.1, 3.1, 1.0 Hz), 88.2 (ddd, *J* = 14.5, 10.8, 2.1 Hz). FT-IR cm^{-1} 3414, 3357, 2924, 2234, 1642. GC/MS (*m/z*, relative intensity) 172 (M+, 100), 145(15), 125 (20), 75 (20). mp 82-86 ^{o}C.

Synthesis of 2.7m (2-(2,3,5,6-tetrafluorophenyl)benzo[d]oxazole)



The general procedure A was followed using 2-(perfluorophenyl)benzo[d]oxazole (29 mg, 0.10 mmol), *i*Pr$_2$NEt (43 mg, 0.33 mmol) and 1 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN. After 24 hours, preparative TLC (hexane: EtOAc 90:10, 1% acetic acid) was used to isolate **2.7m** in 83% (22 mg, 0.083 mmol) as a light yellow solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.6 – -137.8 (m, 2F), -138.0 – -138.2 (m, 2F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (dd, *J* = 85.7, 1.8 Hz, 1H), 7.96 – 7.63 (m, 1H), 7.46 (dd, *J* = 7.3, 1.2 Hz, 2H), 7.29 (dd, *J* = 9.2, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.3 – 153.1 (m), 150.7, 147.9 – 147.6 (m), 146.7 – 143.8 (m), 145.3 (dt, *J* = 243.4, 3.7 Hz), 141.3, 126.7, 125.3, 121.1, 111.2, 108.9 (t, *J* = 22.4 Hz). FT-IR cm^{-1} 3001, 1653, 1551, 1653. GC/MS (*m/z*, relative intensity) 267 (M+, 100), 239 (25), 92 (20), 64 (60). mp 108-110 ^{o}C.

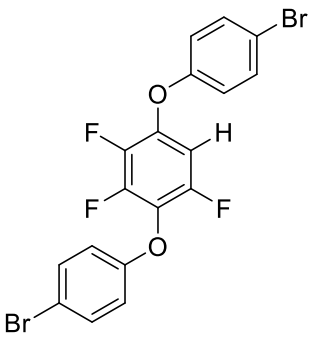
Synthesis of 2.7n (*N*,*N*-dimethyl-1-(4,5,7-trifluoro-2-phenylbenzofuran-3-yl)methanamine)



The general procedure B was followed at 65 ^{o}C using *N*,*N*-dimethyl-1-(4,5,6,7-tetrafluoro-2-phenylbenzofuran-3-yl)methanamine (24 mg, 0.75 mmol), *i*Pr$_2$NEt (32 mg, 0.33 mmol) and 0.75 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used. The crude material was

purified by flash chromatography using hexane : ethyl acetate (0 – 8% EtOAc for 5 cv and ramped to 100 % EtOAc for 8-20 cv and then held at 100% EtOAc 20-25 cv) on a 24 g silica column) to afford **2.7n** in 65% yield (20 mg, 0.065 mmol) as a colorless liquid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.4 (dd, *J* = 19.7, 9.5 Hz, 1F), -143.9 (dd, *J* = 21.0, 10.7 Hz, 1F), -151.5 (td, *J* = 20.3, 5.7 Hz, 1F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (t, *J* = 7.6 Hz, 2H), 7.51 (m, 3H), 6.92 (td, *J* = 10.1, 6.0 Hz, 1H), 3.68 (s, 2H), 2.35 (s, 6H). ^{13}C NMR (600 MHz, Chloroform-*d*) δ 156.6, 146.6 – 144.6 (m), 144.0 – 141.8 (m), 140.3 (ddd, J = 248.4, 15.2, 3.8 Hz), 138.00, 130.06 – 127.86 (m), 128.12 (d, J = 29.8 Hz), 123.06 (d, J = 14.5 Hz), 113.65, 96.2, 101.47, 52.86, 45.33. FT-IR cm^{-1} 3063, 2987, 1601, 1245, 1421. GC/MS (*m/z*, relative intensity) 305 (M+, 305), 290 (80), 261 (100), 232 (30).

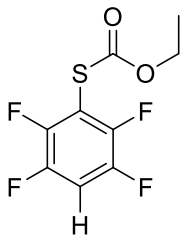
Synthesis of 2.7o (4,4'-((2,3,5-trifluoro-1,4-phenylene)bis(oxy))bis(bromobenzene))



The general procedure B was followed at 65 °C in an NMR tube using 4,4'-((perfluoro-1,4-phenylene)bis(oxy))bis(bromobenzene) (49 mg, 0.10 mmol), *i*Pr$_2$NEt (43 mg, 0.33 mmol) and 1.0 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used. The crude material was purified by flash chromatography using hexane with 1% AcOH : ethyl acetate (0-5 % EtOAc for 40 cv and ramped to 100 % EtOAc for 40-70 cv and then held at 100% EtOAc 70-80 cv) on a 24 g silica column to afford **2.7o** in 50% isolated (24 mg, 0.050 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -130.0 (t, *J* = 10.5 Hz, 1F), -146.4 (dd, *J* = 19.9, 2.1 Hz, 1F), -156.3 (ddd, *J* = 19.8, 10.3, 7.0 Hz, 1F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 30.4, 9.0 Hz, 4H), 6.83 (dd, *J* = 33.6, 8.9 Hz, 4H), 6.60 (ddd, *J* = 10.6, 7.0, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.59, 154.94, 152.58 – 149.85 (m), 147.97 – 144.29 (m), 142.28 – 138.72 (m), 133.13, 132.75 (d, *J* = 56.9 Hz), 132.69 (d, *J* = 5.5 Hz), 128.69 – 128.06 (m), 120.01, 117.35, 117.14, 115.90,

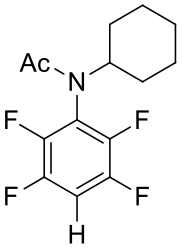
103.30 (dd, *J* = 23.5, 3.3 Hz). FT-IR cm^{-1} 3047, 1593, 1551, 1267. GC/MS (*m/z*, relative intensity) 474 (M+, 100), 365 (20), 222 (10), 155 (32), 76 (60). mp 84-86 °C.

Synthesis of 2.7p (*O*-ethyl *S*-(2,3,5,6-tetrafluorophenyl) carbonothioate)



The general procedure A was followed using *O*-ethyl *S*-(perfluorophenyl) carbonothioate (54 mg, 0.20 mmol), *i*Pr_2NEt (28 mg, 0.22 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2o** in 72% ^{19}F NMR yield and 50% isolated yield (26.0 mg, 0.10 mmol). The crude material was purified by flash chromatography using hexane : DCM (0 % DCM for 10 cv and ramped slowly to 30 % DCM for 10-30 cv and then held at 35% DCM 30-35 cv) on a 24 g silica column. to obtain a mixture of para (90%) and ortho (10%) mono-HDF as a colorless liquid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -131.7 – -131.8 (m, 2F), -137.7 – -137.9 (m, 2F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (tt, *J* = 9.6, 6.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.8, 148.1 – 145.3 (m), 147.2 – 144.2 (m), 109.8 – 107.5 (m), 109.29 , 65.97, 14.06. FT-IR cm^{-1}3023, 2978, 1736, 1524, 1642. GC/MS (*m/z*, relative intensity) 255 (M+, 2), 209 (8), 182 (100), 137 (35).

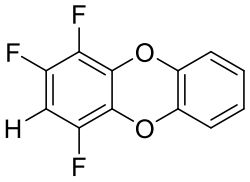
Synthesis of 2.7q (*N*-cyclohexyl-*N*-(2,3,5,6-tetrafluorophenyl)acetamide)



The general procedure C was followed using *N*-cyclohexyl-*N*-(perfluorophenyl)acetamide (25 mg, 0.080 mmol), *i*Pr_2NEt (43 mg, 0.33 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN. The crude material was purified by flash chromatography using hexane : diethyl ether (0 % for 1 cv, slowly ramped to 25 % ether for 1-35 cv, to 100% ether for 35-54 cv, then held at 100% ether 54-57 cv), on a 24 g silica column to afford **2.7q** in 61% (adjusted) yield (15 mg, 0.050 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.4 (dt, *J* = 21.9, 10.9 Hz, 2F), -142.0 – -142.2 (m, 2F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (tt, *J* = 9.6, 7.2 Hz, 1H), 4.52 (tt, *J* =

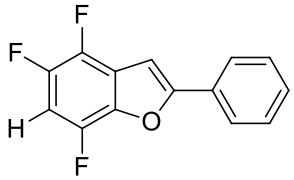
12.1, 3.6 Hz, 1H), 1.75 (s, 3H), 1.93 – 1.49 (m, 4H), 1.39 – 0.86 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.6, 147.9 – 145.8 (m), 145.5 – 143.3 (m), 121.1 – 120.5 (m), 106.9 (t, *J* = 22.7 Hz), 56.2, 29.9, 25.8, 25.5, 22.8. FT-IR cm^{-1} 3043, 2924, 1678, 1505, 1306. GC/MS (*m/z*, relative intensity) 289 (M+, 3), 247 (15), 207 (53), 165 (42). mp 120-124 °C.

Synthesis of 2.7r (1,2,4-trifluorodibenzo[*b,e*][1,4]dioxine)



The general procedure A was followed using 1,2,3,4-tetrafluorodibenzo[*b,e*][1,4]dioxine (26 mg, 0.10 mmol), *i*Pr$_2$NEt (43 mg, 0.33 mmol) and 2 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used to afford **2.7r** in 45% (at 60% conv.) isolated yield (11 mg, 0.046 mmol) as a white solid. (Prep TLC with 100% hexanes). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.1 (t, *J* = 10.1 Hz), -141.97 (dd, *J* = 21.6, 10.2 Hz), -163.44 (ddd, *J* = 21.6, 10.0, 6.8 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 – 6.96 (m, 4H), 6.63 (td, *J* = 10.2, 6.7 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.2 – 144.2 (m), 143.8 (dd, *J* = 12.0, 3.8 Hz), 140.2 (d, *J* = 40.7 Hz), 136.2 (ddd, *J* = 247.5, 16.6, 4.7 Hz), 133.4 (d, *J* = 12.3 Hz), 133.1 (d, *J* = 6.7 Hz), 128.4, 128.3 (d, *J* = 4.2 Hz), 128.1, 124.9 (d, *J* = 27.8 Hz), 116.7, 99.0 (t, *J* = 23.1 Hz). FT-IR cm^{-1} 3056, 1600, 1524, 1244. GC/MS (*m/z*, relative intensity) 238 (M+, 100), 209 (10), 182 (22), 50 (20). mp 108-112 °C.

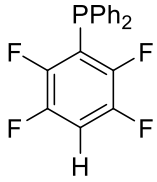
Synthesis of 2.7s (4,5,7-trifluoro-2-phenylbenzofuran)



The general procedure B was followed at 65 °C using 4,5,6,7-tetrafluoro-2-phenylbenzofuran (27 mg, 0.10 mmol), *i*Pr$_2$NEt (43 mg, 0.33 mmol) and 1 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used to afford **2.7s** in 76% ^{19}F NMR yield, and 69% isolated yield (18 mg, 0.076 mmol). The crude material was purified by flash chromatography using hexane : ethyl acetate (0 – 8% EtOAc for 5 cv and ramped to 100 % EtOAc for 8-20 cv and then held at 100% EtOAc 20-25 cv) on a 24 g silica column to obtain a mixture of mono HDF products in a 90:10 ratio as a white solid. ^{19}F

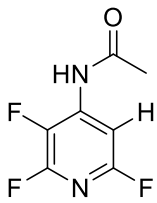
NMR (376 MHz, Chloroform-*d*) δ -138.9 (ddd, *J* = 19.8, 9.7, 2.4 Hz, 1F), -143.6 (dd, *J* = 20.5, 10.7 Hz, 1F), -150.3 (td, *J* = 20.2, 6.0 Hz, 1F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dt, *J* = 6.1, 1.3 Hz, 2H), 7.52 – 7.40 (m, 3H), 7.15 (d, *J* = 2.6 Hz, 1H), 6.92 (ddd, *J* = 10.7, 9.7, 6.0 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.4, 145.0 (ddd, *J* = 241.9, 12.8, 9.3 Hz), 143.4 (dd, *J* = 10.8, 3.5 Hz), 141.8 (dd, *J* = 10.8, 3.4 Hz), 139.8 (dd, *J* = 15.0, 4.5 Hz), 138.1 (d, *J* = 4.5 Hz), 129.7, 129.7, 128.93, 128.88, 125.3, 121.7 (dt, *J* = 19.5, 3.4 Hz), 100.7 (dd, *J* = 24.8, 22.2 Hz), 98.1. FT-IR cm^{-1} 3017, 2128, 1521, 1476, 1422, 1214. GC/MS (*m/z*, relative intensity) 248 (M+, 100), 219 (44), 201 (13), 124 (10). mp 59-64 ^{o}C.

Synthesis of 2.7t (diphenyl(2,3,5,6-tetrafluorophenyl)phosphane)



The general procedure B was followed at 45 ^{o}C using (perfluorophenyl)diphenylphosphane (35 mg, 0.10 mmol), *i*Pr$_2$NEt (43 mg, 0.33 mmol) and 1 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used to afford **2.7t** in 76% yield by ^{19}F NMR after adding trifluoroacetic acid (0.033 mmol, 2.5 µL). ^{19}F NMR (376 MHz, Benzene-d_6) δ -130.8 – -131.1 (m, 2F), -140.2 – -140.4 (m, 2F). FT-IR cm^{-1} 3013, 2985, 1634, 1475. GC/MS (*m/z*, relative intensity) 334 (M+, 100), 183 (24), 154 (23).

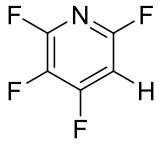
Synthesis of 2.7u (*N*-(2,3,6-trifluoropyridin-4-yl)acetamide)



The general procedure A was followed using *N*-(perfluoropyridin-4-yl)acetamide (42 mg, 0.2 mmol), *i*Pr$_2$NEt (85 mg, 0.66 mmol) and 2 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used to afford **2.7u** in 97% isolated yield (37 mg, 0.19 mmol) as a yellow solid. The crude material was purified by flash chromatography using hexane : ethyl acetate (0-40 % EtOAc for 25 cv and ramped to 100 % EtOAc for 25-50 cv and then held at 100% EtOAc 50-55 cv) on a 24 g silica column. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.7 (dd, *J* = 22.8, 13.3 Hz, 1F), -89.3 (dd, *J* = 21.6, 13.3 Hz, 1F), -165.7 (t, *J* = 22.3 Hz, 1F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.93 (m, 1H), 2.31 (s,

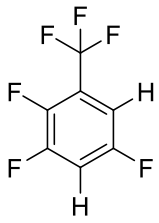
3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.5, 155.9 (ddd, *J* = 241.2, 14.5, 3.2 Hz), 148.3 (ddd, *J* = 240.6, 18.2, 14.5 Hz), 139.6 (ddd, *J* = 12.8, 8.1, 4.5 Hz), 132.0 (ddd, *J* = 248.5, 28.0, 6.6 Hz), 97.3 (ddd, *J* = 45.0, 5.7, 1.3 Hz), 24.6. FT-IR cm^{-1}3418, 3050, 2989, 1638,1550. GC/MS (*m/z*, relative intensity) 190 (M+, 9), 162 (30), 148 (100). mp 66-72 °C.

Synthesis of 2.7v (2,3,4,6-tetrafluoropyridine)



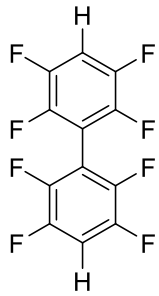
The general procedure B was followed at 45 °C using 3-chloro-2,4,5,6-tetrafluoropyridine (18 mg, 0.10 mmol), *i*Pr$_2$NEt (28 mg, 0.22 mmol) and 1 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used to afford **2.7v** in 78% yield by ^{19}F NMR after adding trifluoroacetic acid (0.025 mmol, 1.9 µL). ^{19}F NMR (376 MHz, Benzene-*d*6) δ -71.4 (d, *J* = 23.1 Hz, 1F), -88.0 (d, *J* = 21.9 Hz, 1F), -116.5 (tdd, *J* = 18.6, 15.4, 8.7 Hz, 1F), -170.7 (tdd, *J* = 22.1, 18.5, 3.8 Hz, 1F). which matches with the literature value (Coe, P. L.; Holton, A. G.; Tatlow, J. C. *J. Fluorine Chem.* **1982**, *21*, 171). FT-IR cm^{-1} 3013, 2985, 1634, 1463.

Synthesis of 2.8a (1,2,5-trifluoro-3-(trifluoromethyl)benzene)



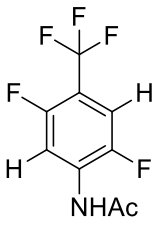
The general procedure A was followed using 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)benzene (24 mg, 0.10 mmol), *i*Pr$_2$NEt (43 mg, 0.33 mmol) and 1.0 mL of stock solution of Ir(ppy)$_3$ in CH$_3$CN was used to afford **2.8a** in 86% yield by ^{19}F NMR after adding trifluoroacetic acid (0.050 mmol, 3.8 µL). ^{19}F NMR (376 MHz, Benzene-d_6) δ -61.6 (d, *J* = 13.2 Hz, 1F), -113.8 (ddd, *J* = 22.7, 8.0, 4.9 Hz, 1F), -132.2 – -132.3 (m, 1F), -146.1 (dddq, *J* = 26.0, 18.8, 13.2, 6.4, 5.1 Hz, 1F). FT-IR cm^{-1}3201, 1653. GC/MS (*m/z*, relative intensity) 200 (M+, 100), 181 (97), 150 (82), 81 (70).

Synthesis of 2.8b (2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl)



The general procedure A was followed using perfluoro-1,1'-biphenyl (67 mg, 0.20 mmol), *i*Pr_2NEt (85 mg, 0.66 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.8b** in 85% isolated yield (50 mg, 0.17 mmol) as a white solid. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % for 19 cv, slowly ramped to 20 % EtOAc for 19-22 cv and then ramped to 100% EtOAc for 22-24 cv, then held at 100% EtOAc 34-40 cv), on a 24 g silica column. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -138.1 – -138.3 (m, 4F), -138.6 – -138.8 (m, 4F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.20 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.0 – 147.5 (m), 145.7 (d, *J* = 14.5 Hz), 145.3 (t, *J* = 11.4 Hz), 143.2 (d, *J* = 13.5 Hz), 108.4 (t, *J* = 22.3 Hz).. FT-IR cm^{-1} 3063, 2988, 1607. GC/MS (*m/z*, relative intensity) 298 (M+, 100), 280 (7), 260 (9), 229 (30). mp 66-74 °C.

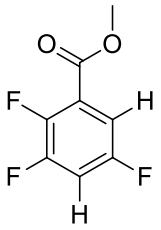
Synthesis of 2.8c (*N*-(2,5-difluoro-4-(trifluoromethyl)phenyl)acetamide)



The general procedure A was followed using *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide (27 mg, 0.10 mmol), *i*Pr_2NEt (78 mg, 0.60 mmol) and 1 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford **2.8c** in 74% isolated yield (17 mg, 0.070 mmol) as a yellow solid. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 – 50% EtOAc for 25 cv and ramped slowly to 100% EtOAc for 25-55 cv and then held at 100% EtOAc for 55-58 cv) on a 24 g silica column). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.4 (d, *J* = 12.6 Hz, 3F), -116.5 (ddt, *J* = 18.3, 12.6, 6.0 Hz, 1F), -136.4 – -136.5 (m, 1F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (dd, *J* = 12.3, 6.5 Hz, 1H), 7.49 (s, 1H), 7.33 (dd, *J* = 10.6, 6.2 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.4, 156.0 (d, *J* = 251.2 Hz), 148.0 (d, *J* = 3.1 Hz), 145.6, 130.9, 121.9 (d, *J* = 271.5 Hz), 113.4 – 112.5 (m), 109.5 (dd, *J* = 28.5, 6.9 Hz), 24.8.. FT-IR cm^{-1}3442,

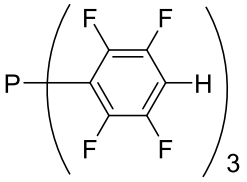
3025, 2977, 1653, 1521. GC/MS (*m/z*, relative intensity) 257 (M+, 6), 215 (40), 192 (17). mp 117-119 °C.

Synthesis of 2.8e (methyl 2,3,5-trifluorobenzoate)



The general procedure A was followed using methyl 2,3,4,5,6-pentafluorobenzoate (23 mg, 0.10 mmol), *i*Pr_2NEt (77 mg, 0.60 mmol) and 1 mL of stock solution Ir(ppy)$_3$ in CH_3CN was used to afford **2.8e** in 73% yield by ^{19}F NMR after adding trifluoroacetic acid (0.025 mmol, 1.9 µL). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -114.9 (dtd, *J* = 15.7, 8.1, 3.5 Hz, 1F), -132.2 – -132.6 (m, 1F), -150.0 – -141.4 (m, 1F). FT-IR cm^{-1} 2963, 1738, 1691, 1468. GC/MS (*m/z*, relative intensity) 190 (M+, 29), 159 (100), 131 (56), 81 (49).

Synthesis of 2.8g (tris(2,3,5,6-tetrafluorophenyl)phosphine)



The general procedure A was followed using tris(pentafluorophenyl)phosphine (106 mg, 0.200 mmol), *i*Pr_2NEt (387 mg, 3.00 mmol) and 2 mL of stock solution of Ir(ppy)$_3$ in CH_3CN was used to afford **2.8g** in 78% isolated yield (75 mg, 0.16 mmol) as a white solid. The crude material was purified by flash chromatography using hexane : ethyl acetate (0% EtOAc for 0-1 cv, 0%-15% EtOAc for 1-10 cv, 15% EtOAc for 10-18 cv, 15%-80% EtOAc for 18-23 cv, 80% EtOAc for 23-30 cv, 80%-100% EtOAc for 30-32 cv, then held at 100% EtOAc 32-35 cv), on a 40 g silica column. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -130.9 – -131.1 (m, 6F), -137.7 (dd, *J* = 16.7, 8.5 Hz, 6F). ^{1}H NMR (400 MHz,Chloroform-*d*) δ 7.18 – 7.05 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.4 (dtt, *J* = 244.8, 11.2, 11.2, 5.1, 5.1 Hz), 146.0 (ddd, *J* = 249.6, 9.6, 3.9 Hz), 111.8 – 108.6 (m), 109.1 (t, *J* = 22.5, 22.5 Hz). FT-IR cm^{-1} 3050, 1603, 1550, 1490, 1368, 1245. GC/MS (*m/z*, relative intensity) 478 (M+, 100), 329 (40), 260 (36). mp 74-77 °C.

Catalyst turnover experiment and calculation

To assess the catalyst robustness the following TON experiment was carried out using pentafluoropyridine as the substrate. An NMR tube was charged with *tris*(2- phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.00001 mmol in 0.5 mL of MeCN-d_3 made *via* serial dilution) and fitted with rubber septum (Ace glass, part no. 9096-25), pentafluoropyridine (0.05 mmol, 5.5 µL, 1 equiv) and *i*Pr_2NEt (0.25 mmol,44.1µL,5 equiv) were added. The reaction was degassed *via* Ar bubbling (at 0 °C) for 5-10 min and septum was parafilmed tightly to avoid exposure to air. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 45 °C. The reaction progress was monitored periodically by ^{19}F NMR. A mixture of pentafluoropyridine and *i*Pr_2NEt (1:1 mol:mol) prepared and degassed in a 12 x 75 mm borosilicate test tube fitted with rubber septum. Seven portions of the above mixture were added over a 96 hour period. A total of 0.275 mmol pentafluoropyridine (**2.7a'**) and 0.475 mmol *i*Pr_2NEt were added. After the each addition, the NMR tube was degassed *via* Ar bubbling for 5-10 min in an ice bath and the septum was again parafilmed. After 96 hours detectable quantities of byproducts were observed in the ^{19}F NMR. The reaction was quenched by exposing it to air and ^{19}F NMR yield was obtained after adding trifluoroacetic acid (0.15 mmol, 11.5 µL) as internal standard.

The TON was calculated as follows. [0.275 mmol (**2.7a'**)/0.00001 mmol ($Ir(ppy)_3$)]*0.82(yield) =22,550 TON.

HDF in flow reactor

Pentafluoropyridine (2.7a') as the substrate

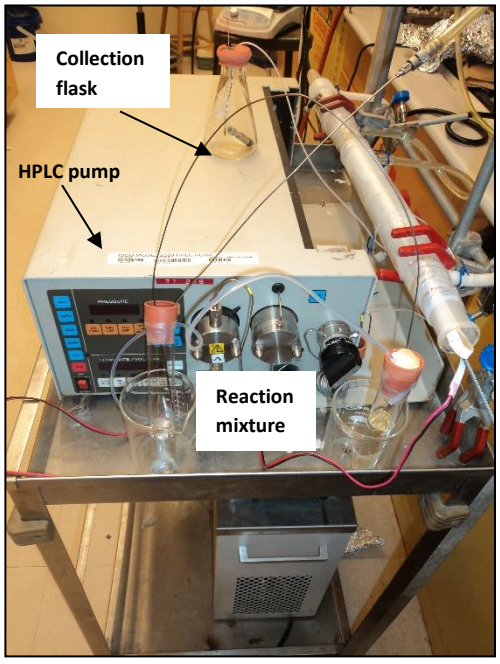
A flow reactor was fabricated in following way. A reflux condenser was wrapped with polyalkoxyteflon tubing (ID= 1.58 mm, 22.5 ft, 13.6 mL). Blue LED strips facing outwards were placed within the condenser. A heated (45 °C) mixture of water and ethylene glycol, which was

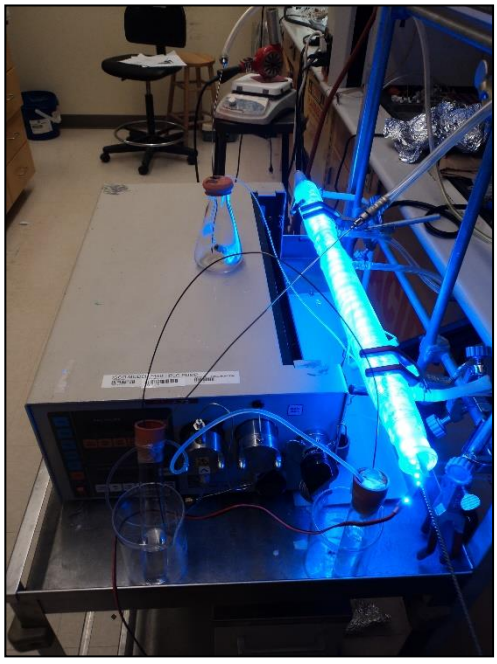
colorless, was passed through the system to maintain a constant temperature. One end of polyalkoxyteflon tubing was connected to the HPLC pump and other end was directed to an empty collection flask. The reaction flask was joined to the inlet of HPLC pump. Before the reaction commencement the reaction tube and collection tube were flushed with Ar (15 min) and the tubing was flushed with degassed MeCN (50 mL). The reaction mixture of pentafluorpyridine (3 mmol, 0.33 mL, 1equiv), *tris*(2- phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.0068 mmol, 5.4 mg) and *i*Pr_2NEt (12 mmol, 2.0 mL, 4 equiv) in MeCN (30 mL) was degassed in a 25 x 150 borosilicate glass tube capped with rubber septum *via* Ar bubbling for 30 min in an ice bath. The reaction mixture was transferred to the reservoir tube (25 x 150 borosilicate glass tube capped with rubber septum) *via* a cannula and reaction was again degassed for 15 min in an ice bath. The reaction mixture was pumped at 0.01 mL/min through 22.5 ft (total reactor volume= 13.6 mL, residence time 9 hours). Throughout the reaction, both reaction and collection tubes were kept under positive Ar pressure, *via* the use of a bubbler open to atmosphere. After collecting the reaction mixture ^{19}F NMR showed 100% conversion and 82% yield after adding TFA (1.5 mmol, 114 µL).

Octafluornapthelene (2.7c') as the substrate

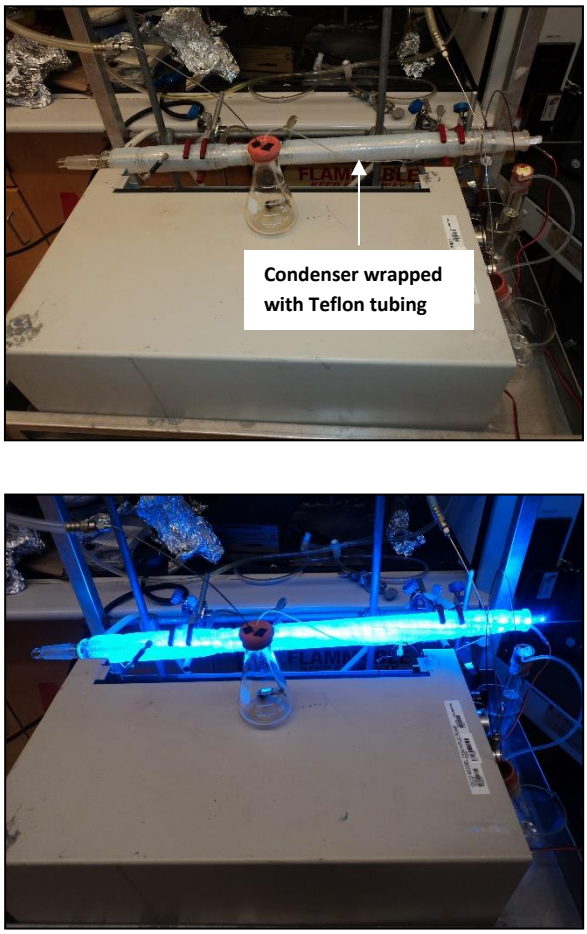
Reaction was carried out in the same way as above with some modifications. Two reflux condensers (in tandem) were wrapped with PFA perfluoroalkoxy tubing (IDEX Health and Science, ID= 0.76 mm, 200 ft, 28 mL) was wrapped tightly around connected condensers. Blue LED strips facing outwards were placed within the condenser. Heated mixture of water (65 ^oC) and ethylene glycol (colorless) was pumped through the system along that flow to maintain a constant temperature. One end of polyalkoxyteflon tubing was connected to the HPLC pump and other end was directed to an empty collection flask. At this temperature, significant gas bubble formation occurred in the reactor line. In order to prevent gas evolution, a standard union was placed on the collection end and a screw-plug was used to regulate the back pressure. The screw

could be used as a valve, wherein by partially closing the opening resulted in back-pressure on the line and prevent the gas evolution and irregularities in the retention time. The reaction flask was joined to the inlet of HPLC pump. Before reaction starts reaction tube and collection tube were flushed with Ar (15 min) and the tubing was flushed with degassed MeCN (50 mL). The reaction mixture of octafluoronapthalene (0.2 mmol, 54 mg, 1equiv), *tris*(2- phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.001 mmol, 0.6 mg) and *i*Pr_2NEt (12 mmol, 2.0 mL, 4 equiv) in MeCN (2.0 mL) was degassed in a 25 x 150 Borosilicate glass tube capped with rubber septum *via* Ar bubbling for 30 min in an ice bath. Reaction mixture was transferred to the reaction tube (25 x 150 borosilicate glass tube capped with rubber septum) as stated above *via* a cannula and reaction was degassed again for 15 min in an ice bath. Reaction mixture was pumped at 0.01 mL/min. Throughout the reaction, both reaction and collection tubes were kept under positive Ar pressure (bubbler). The residence time was 20 hours. After collecting the reaction mixture ^{19}F NMR showed 53% conversion and 51% yield after adding TFA (0.1 mmol, 7.6 µL).





Front view of flow reactor



Lateral view of flow reactor

Deuterium labelling experiment

To determine the source of the H-atom 3 separate NMR tube reactions were performed. First, the HDF-reaction was performed with methyl-2,3,4,5,6-pentafluorobenzoate (**2.7i'**) and *i*Pr_2NEt in MeCN-d_3. Next, the HDF reaction was performed using *N, N* -dicyclohexyl-*N*-ethylamine and finally using *N, N* -dicyclohexyl-*N*-d_5-ethylamine.

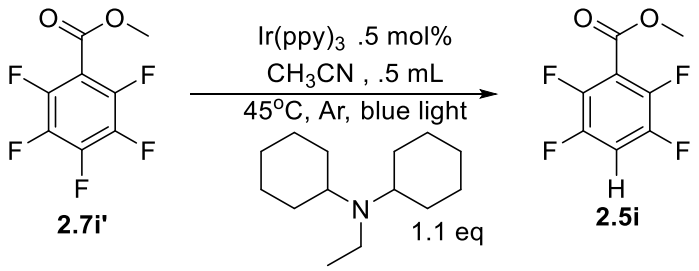
No deuterium in corporation from the solvent occurred. The HDF-reaction proceeds as normal using the alternative and easily isolable amine *N, N* -dicyclohexyl-*N*-ethylamine giving HDF product **2.7i**. This result suggests that a deuterium labeling study should be informative. When the reaction is performed using an analogous deuterium labeled amine, deuterium was

incorporated. This result confirms the amine as the source of the H/D-atom but also reveals that all α-C-H's can be transferred.

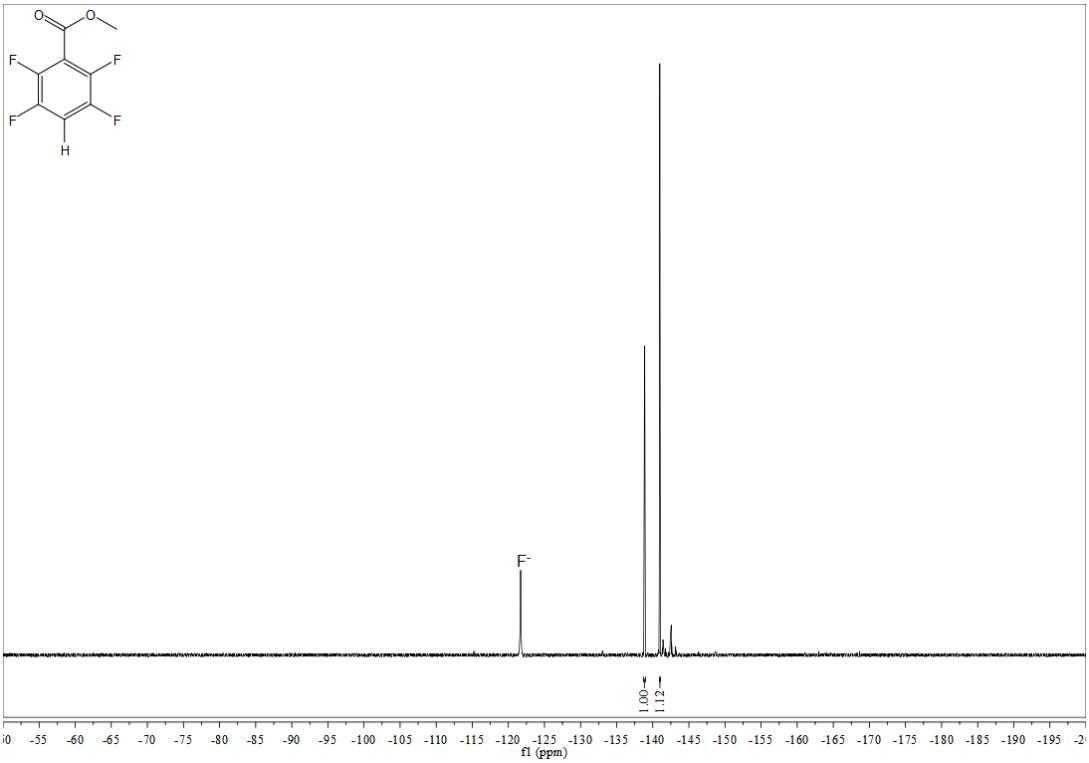
General procedure for deuterium labelling experiment

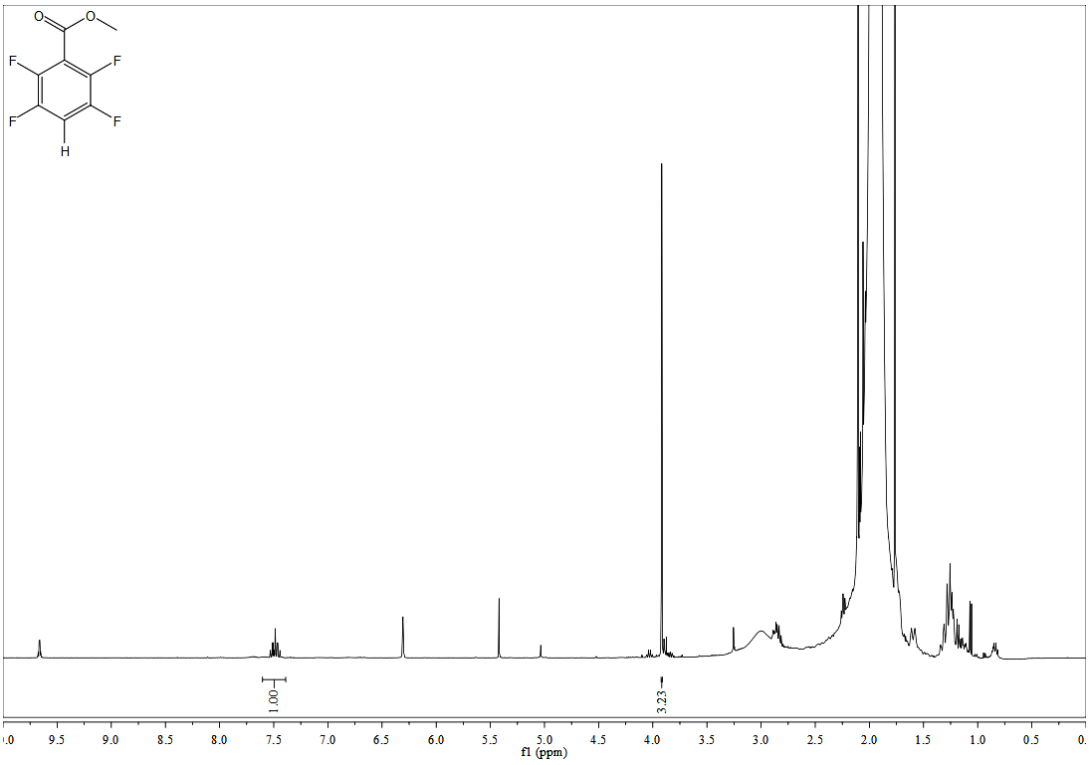
In an NMR tube capped with NMR septa (Ace glass, part no. 9096-25) was charged *tris*(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.5 mM, 0.5 mL in MeCN). Methyl 2,3,4,5,6-pentafluorobenzoate (1 equiv, 11.3 mg, 0.05 mmol) and amine (1.1 equiv, 11.5 mg, 0.055 mmol) were added and sealed glass capillary containing C_6D_6 was placed in NMR tube for locking purposes before degassing. Then the reaction was degassed at 0 °C *via* Ar bubbling for 10 min. The NMR tube was placed in a light bath (*vide supra*) and the lower portion of the tube was submerged under the water bath which was maintained at 45 °C. ^{19}F NMR and GC-MS were recorded after 7 hours.

Reaction with *N, N* -dicyclohexyl-*N*-ethylamine



When *N, N* -dicyclohexyl-*N*-ethylamine was used as the amine and methyl-2,3,5,6-tetrafluorobenzoate (**2.5i**) was detected as the major product by ^{19}F NMR, ^1H NMR and GC-MS, consistent with the normal HDF reaction.


O
O
F
F
F
F
H
F-
1.00
1.12
-55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195
f1 (ppm)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F
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F
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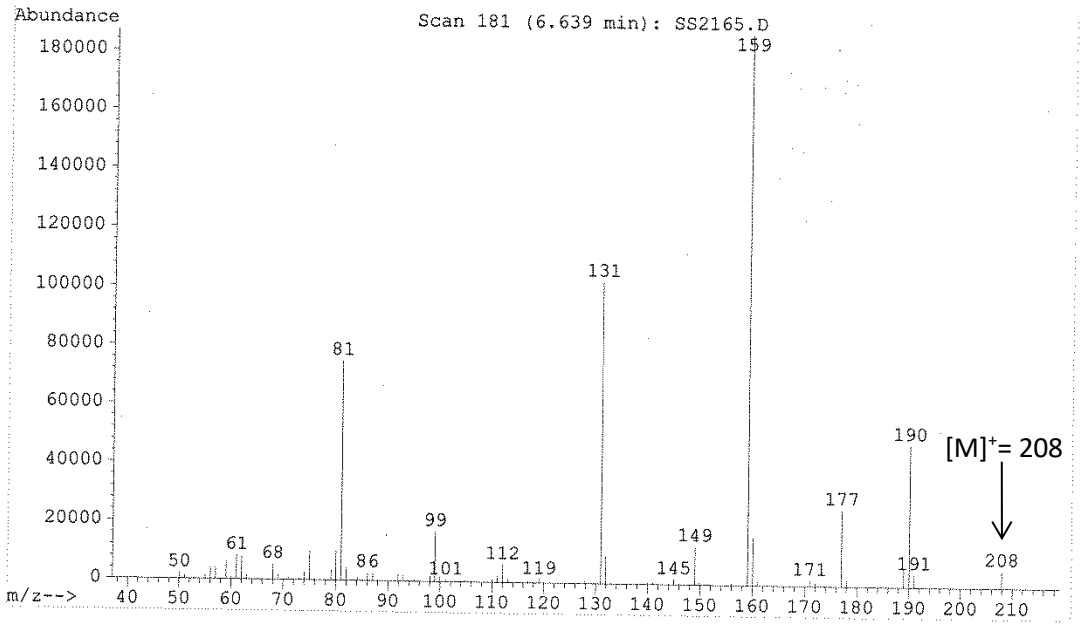
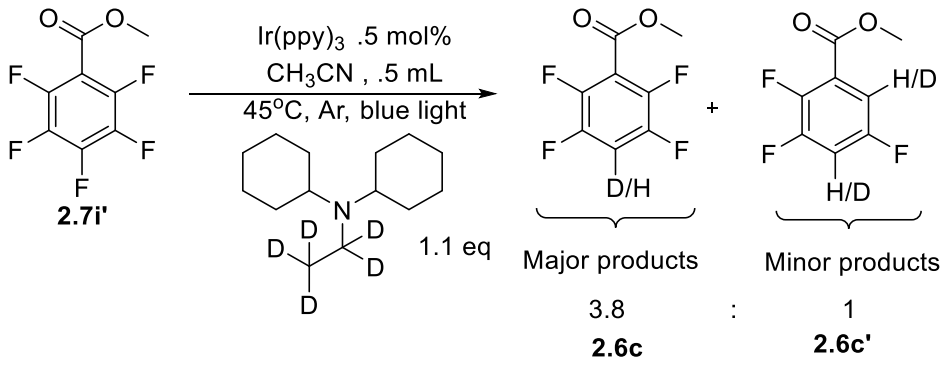
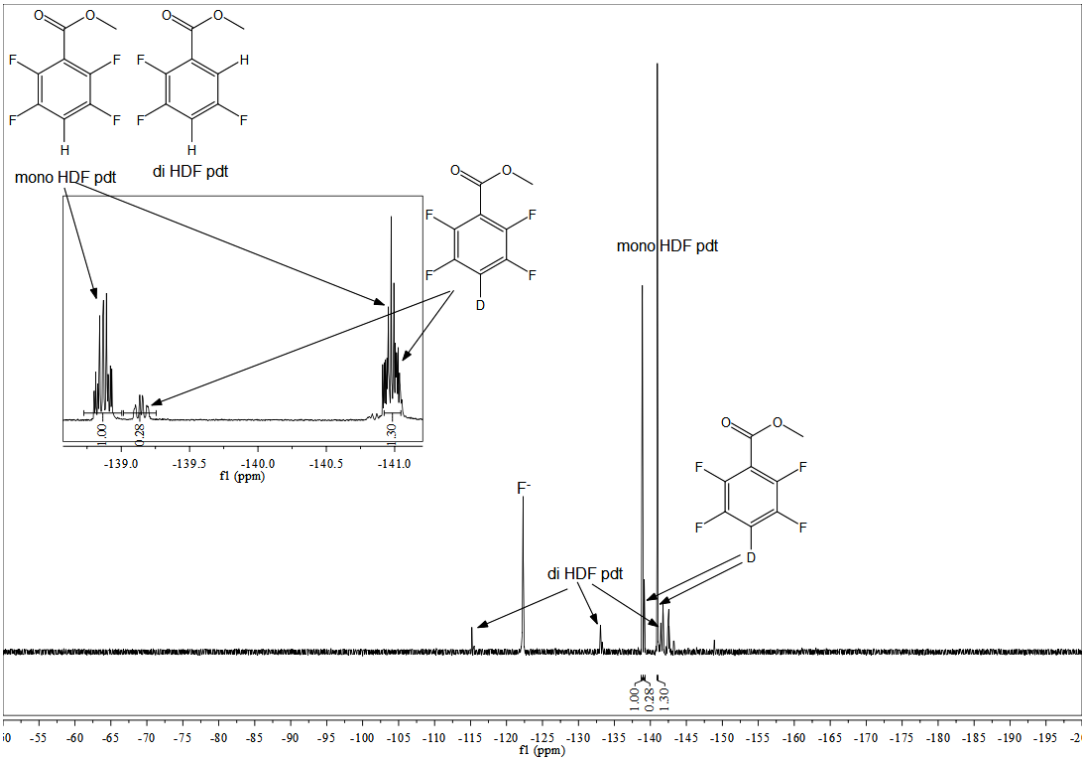
f1 (ppm)

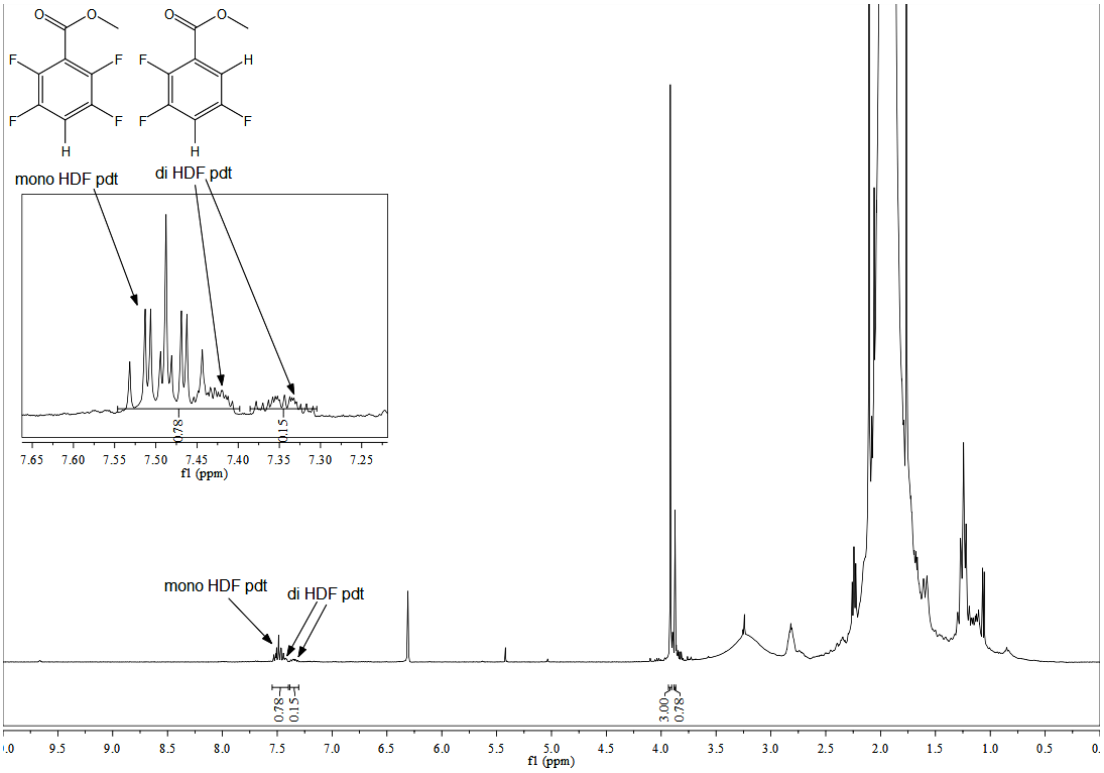


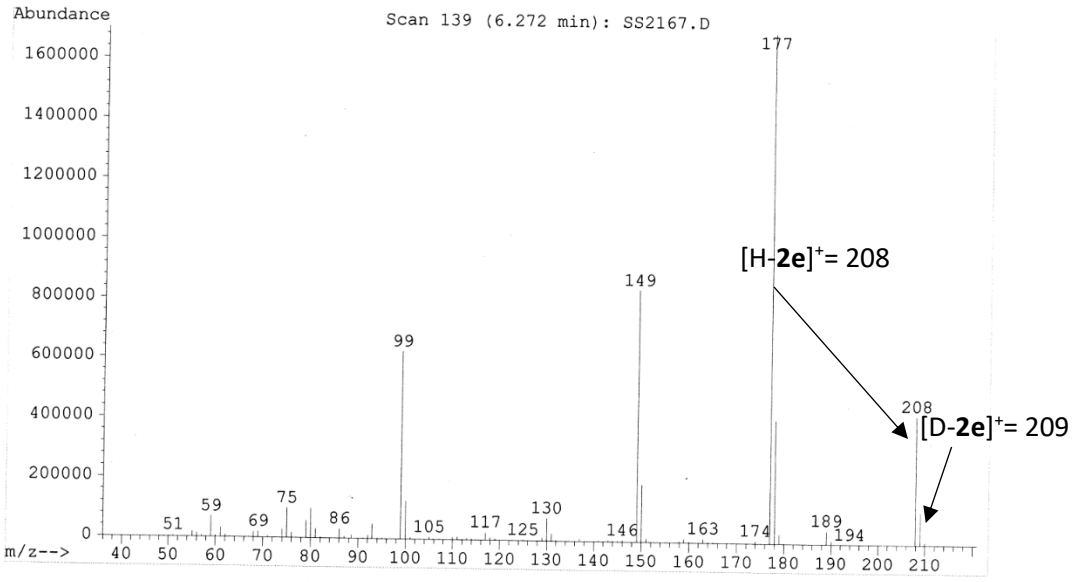
Reaction with *N, N* -dicyclohexyl-*N*-d_5-ethylamine



When *N, N* -dicyclohexyl-*N*-d_5-ethylamine and methyl-2,3,5,6-tetrafluorobenzoate (**1e**) were used, methyl-2,3,5,6-tetrafluorobenzoate (H/D-**2.6c**) in a 2.1/1 H/D ratio were detected as the major products along with di-HDF products (H/D-**2.6c'**) by ^{19}F NMR, ^{1}H NMR and GC-MS. Mono- and di- HDF prodcuts were identified by comparing the ^{19}F and ^{1}H NMR signals of the crude reaction with the ^{19}F and ^{1}H NMR signals of the isolated compounds.


mono HDF pdt
di HDF pdt
F⁻
f1 (ppm)


mono HDF pdt
di HDF pdt
f1 (ppm)


Abundance
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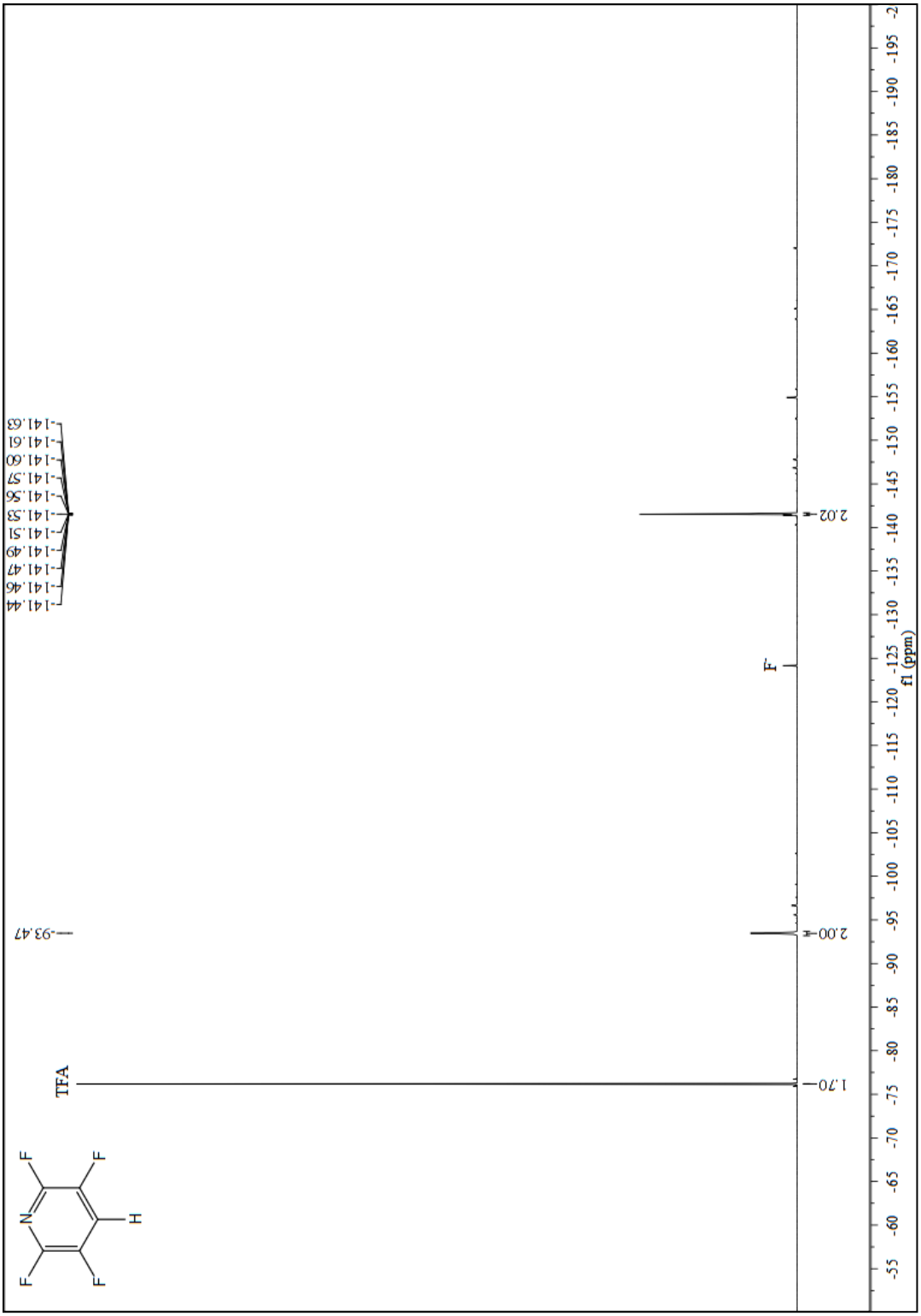
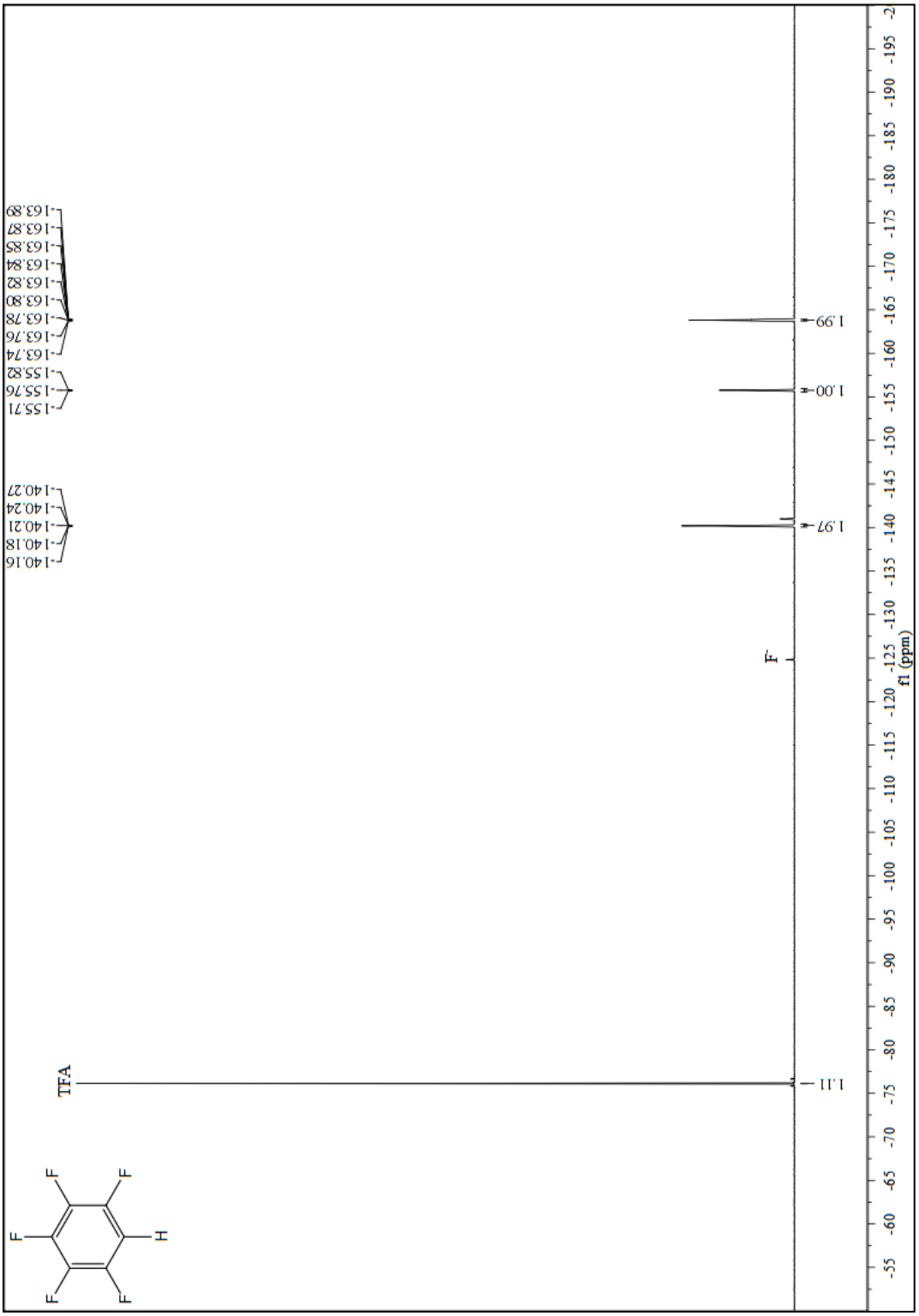
177
149
99
208
59
75
69
86
105
117
125
130
146
163
174
189
194
51
[H-2e]+= 208
[D-2e]+= 209

NMR, GC and MS spectra for Chapter II

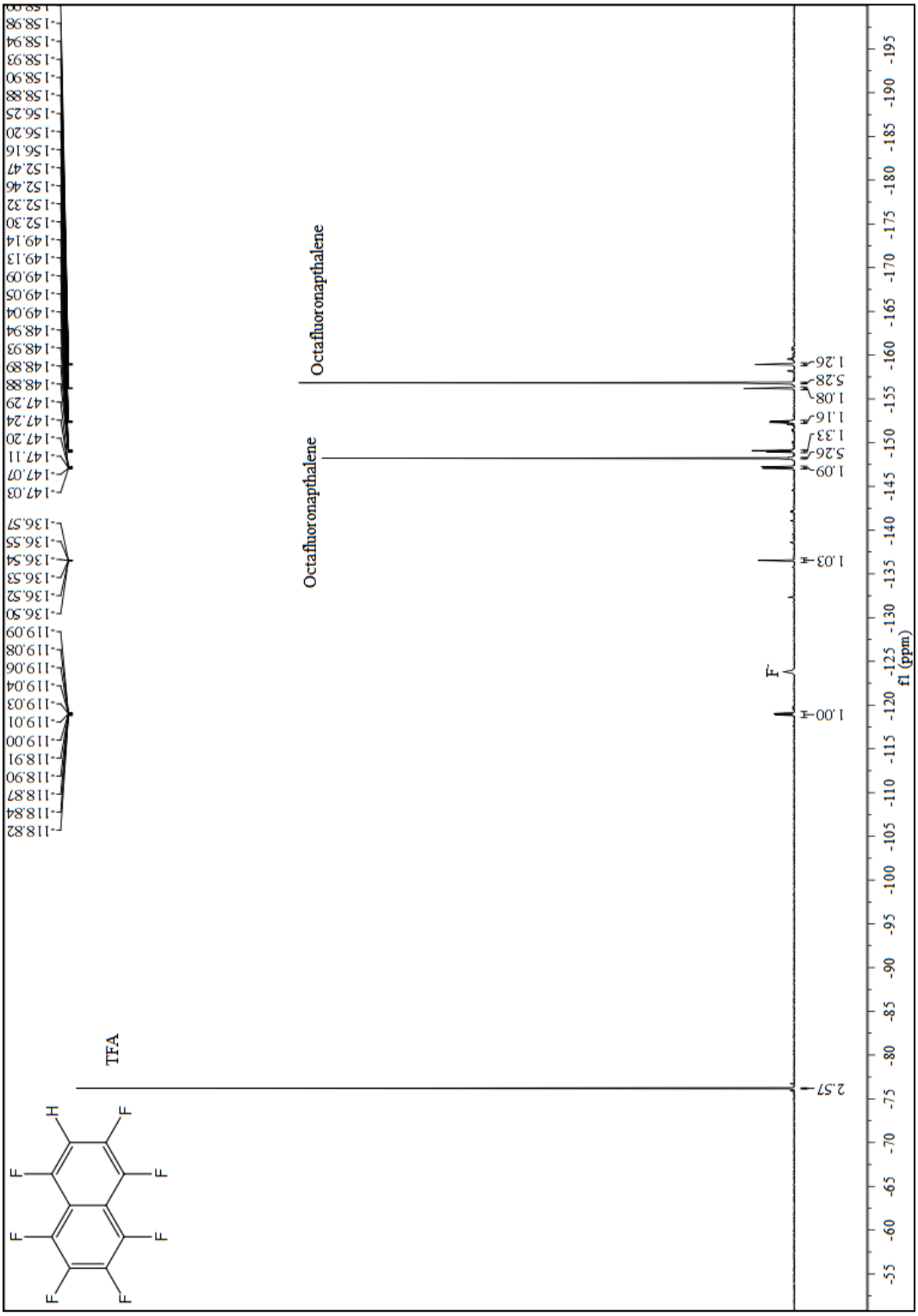
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7a (2,3,5,6-tetrafluoropyridine)



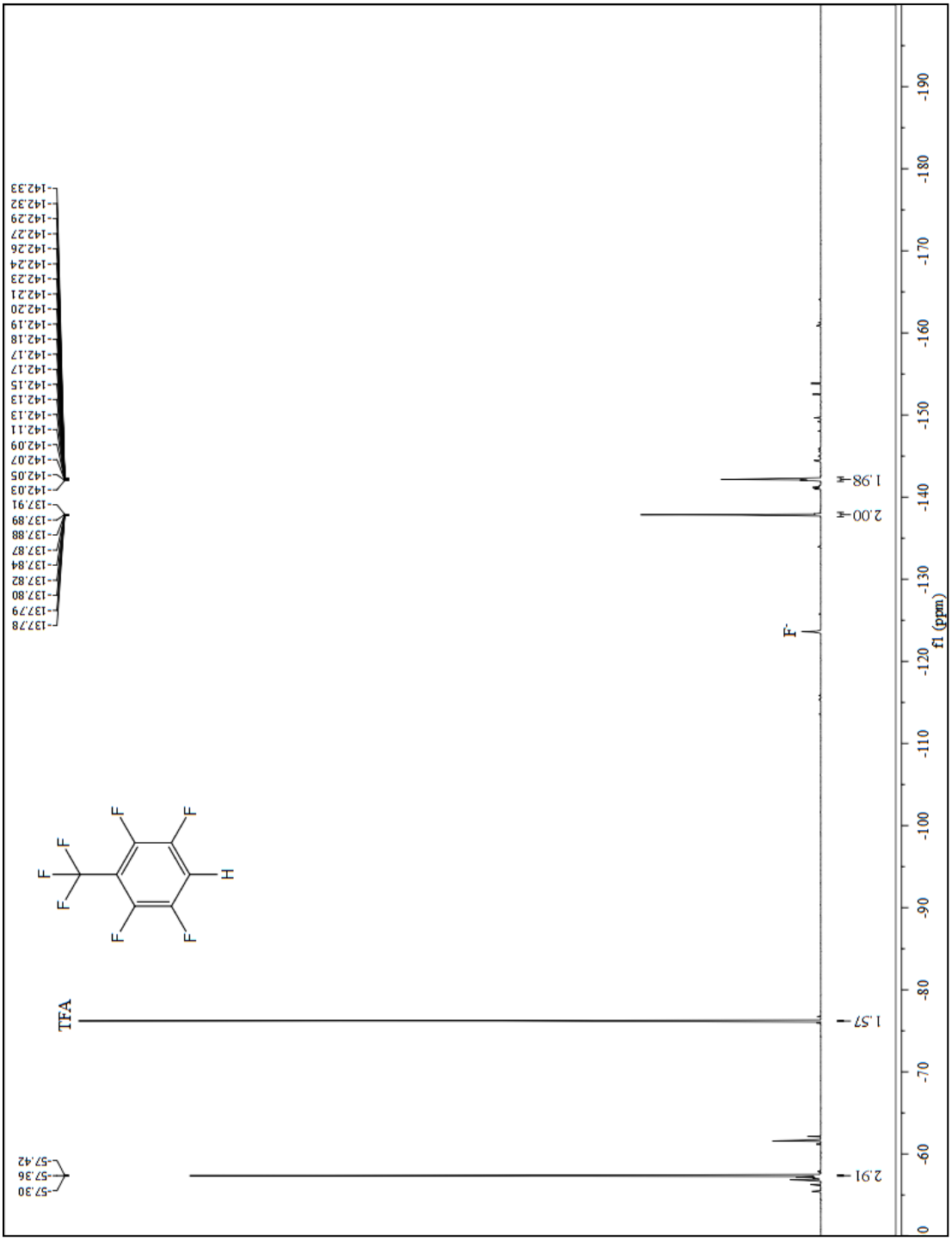
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7b (1,2,3,4,5-pentafluorobenzene)



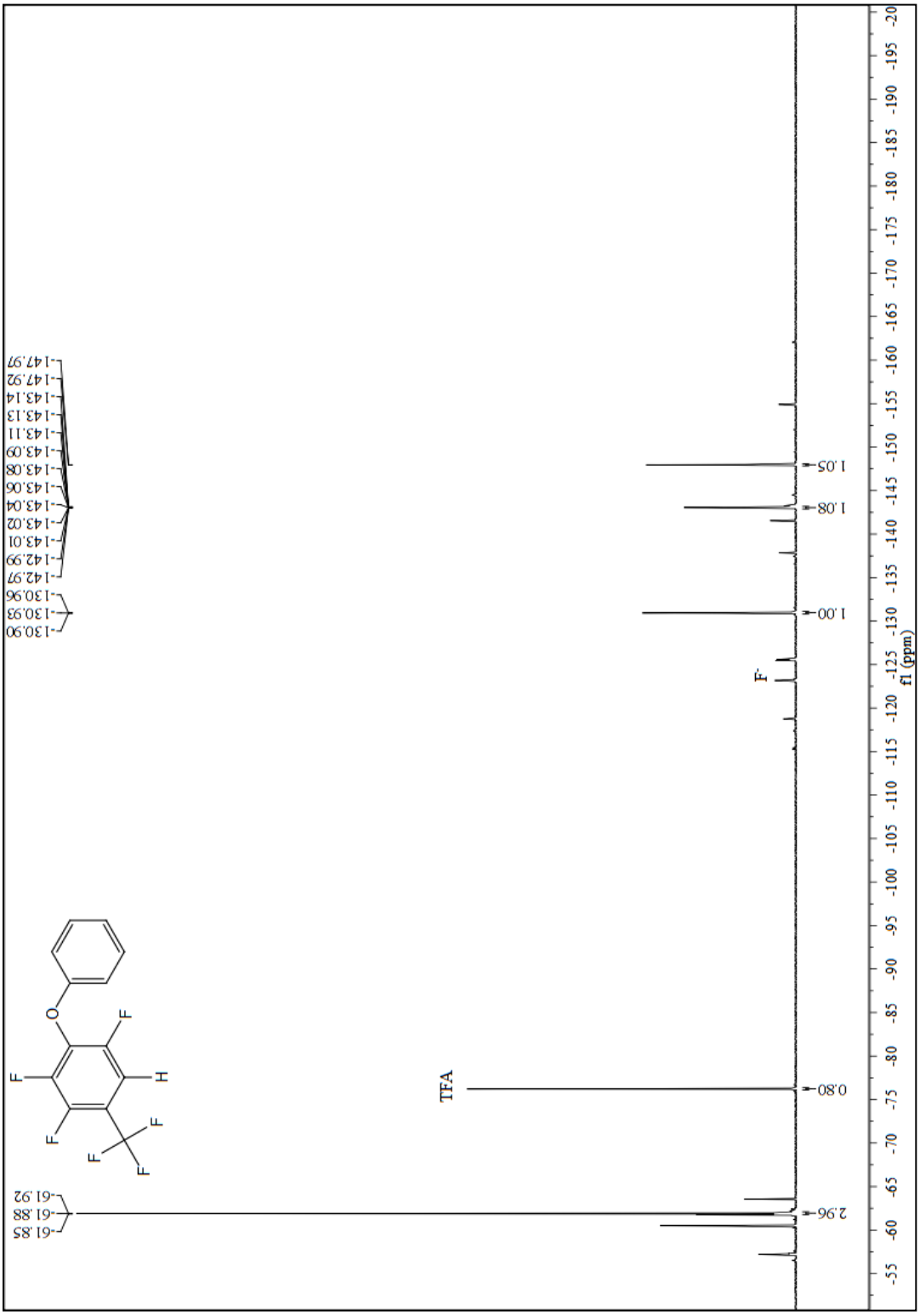
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7c (1,2,3,4,5,6,8-heptafluoronaphthalene)



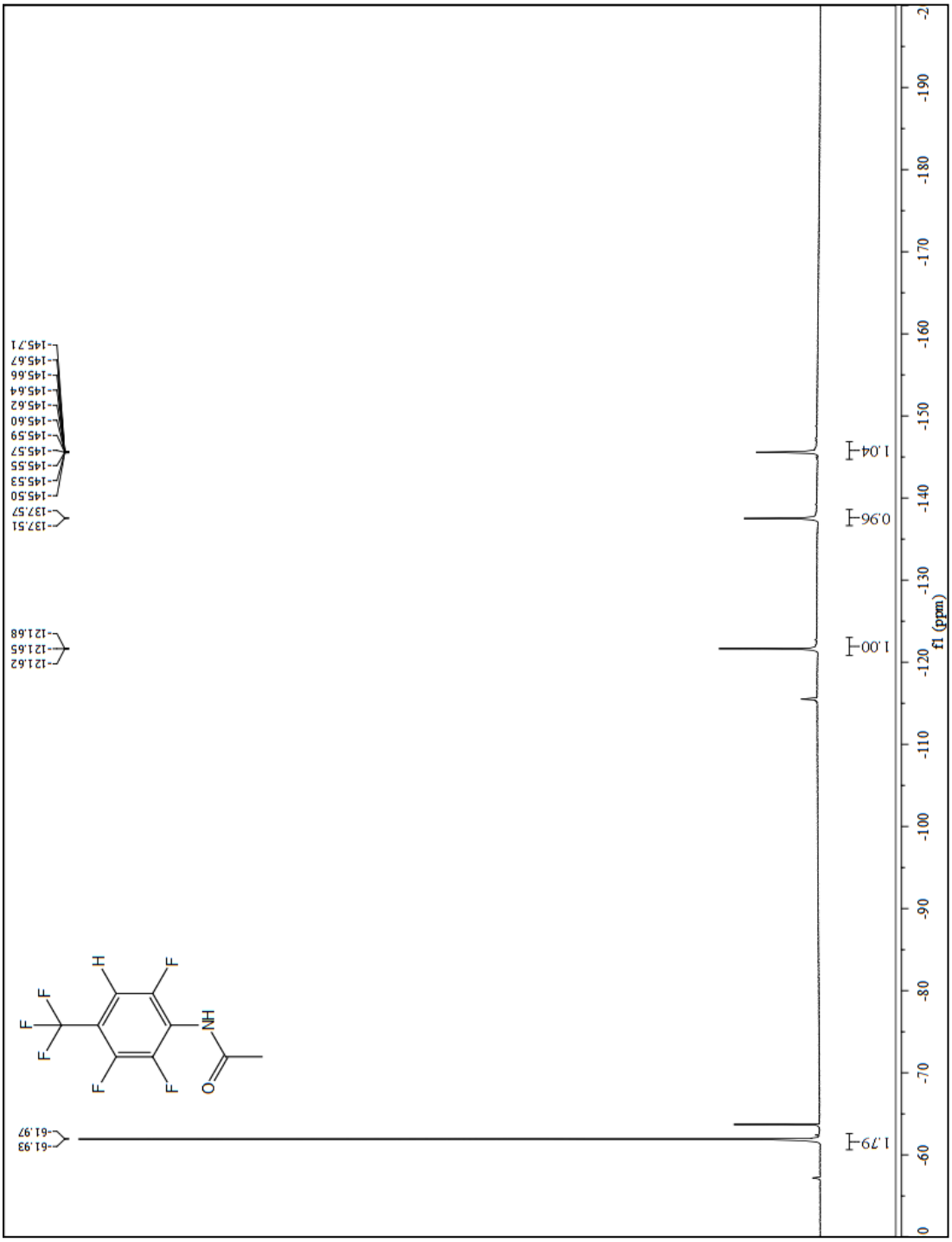
^{19}F NMR (376 MHz, CDCl3, at rt) spectrum of 2.7d (1,2,4,5-tetrafluoro-3-(trifluoromethyl)benzene)



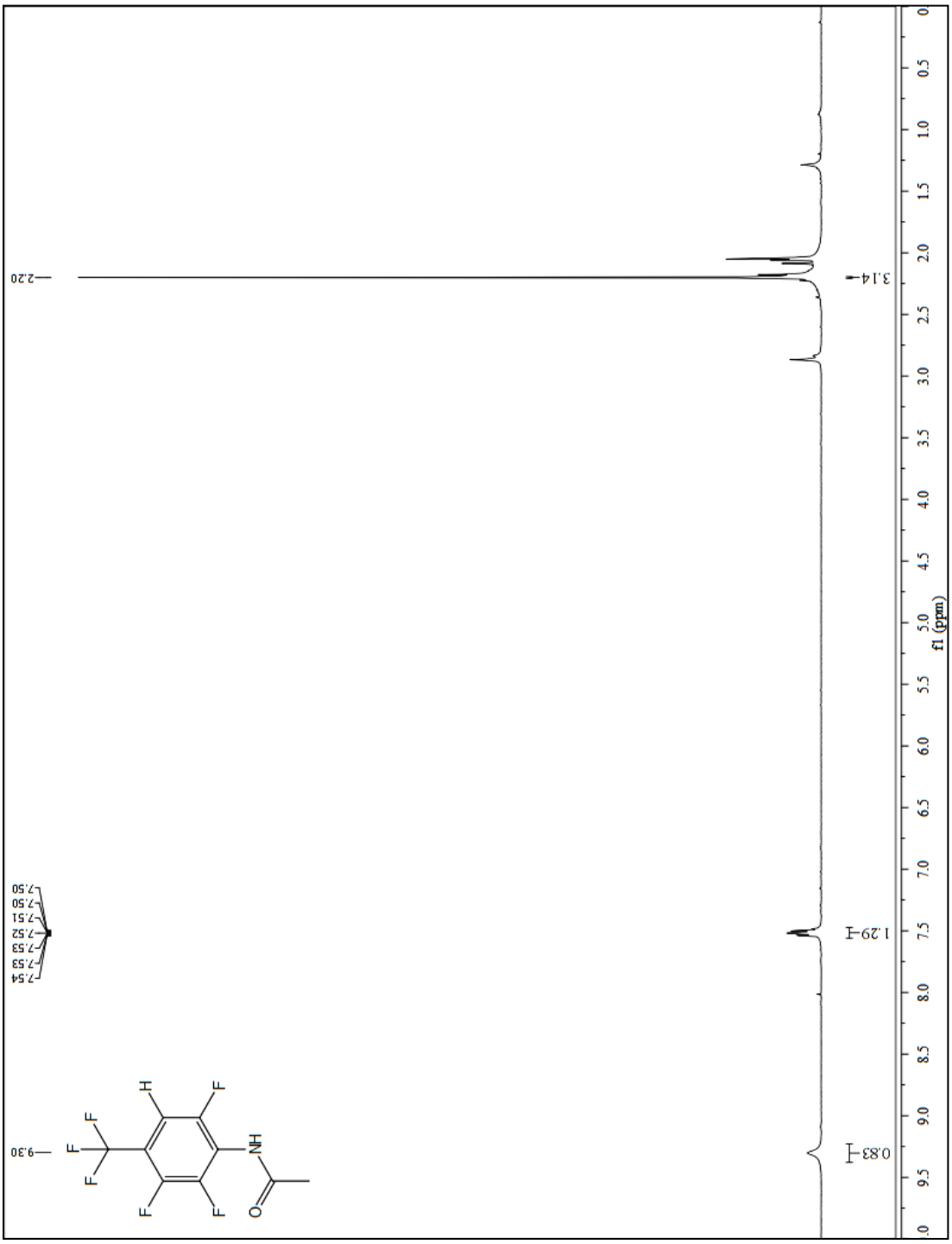
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7e (1,3,4-trifluoro-2-phenoxy-5-(trifluoromethyl)benzene)



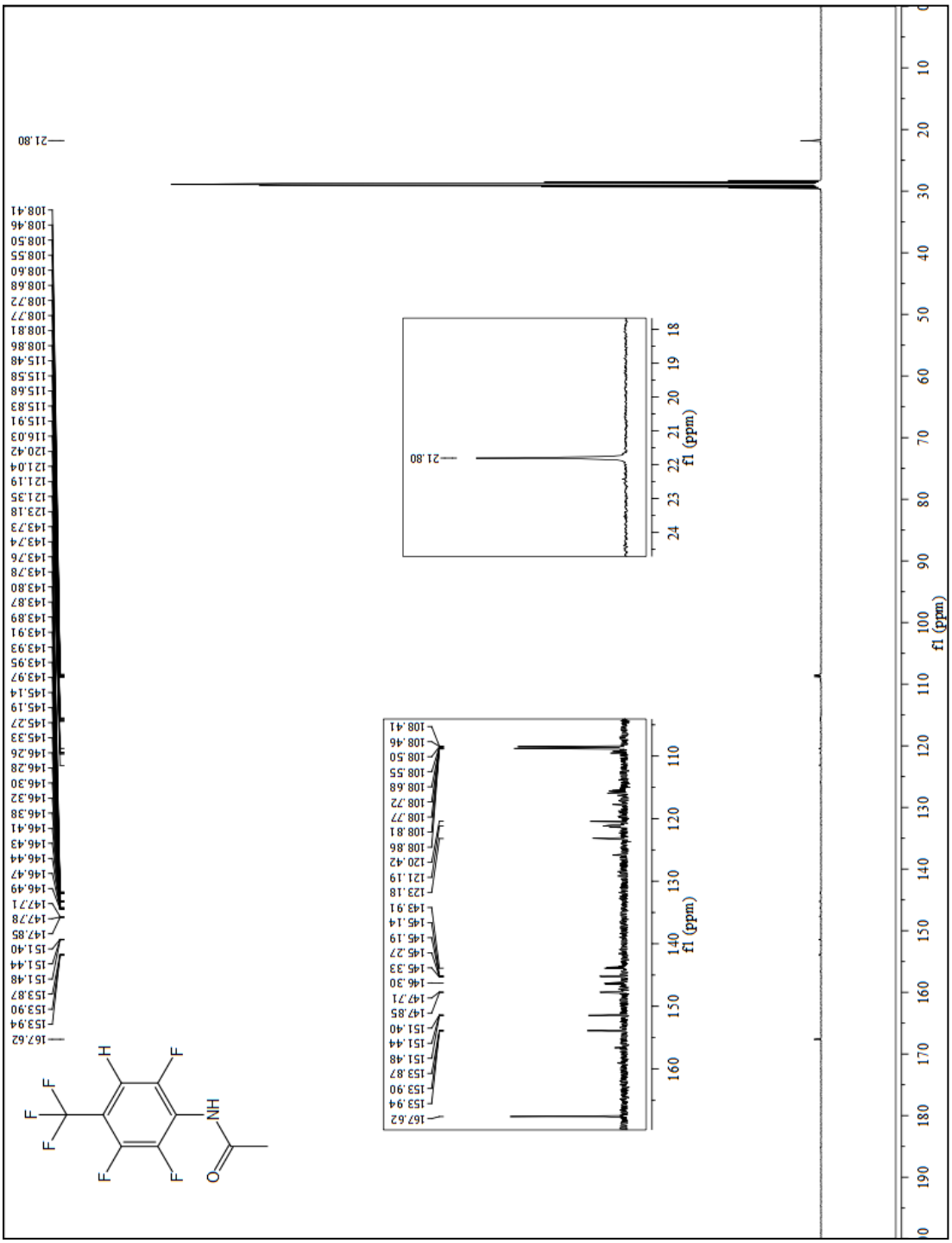
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7f (*N*-(2,3,6-trifluoro-4-(trifluoromethyl)phenyl)acetamide)



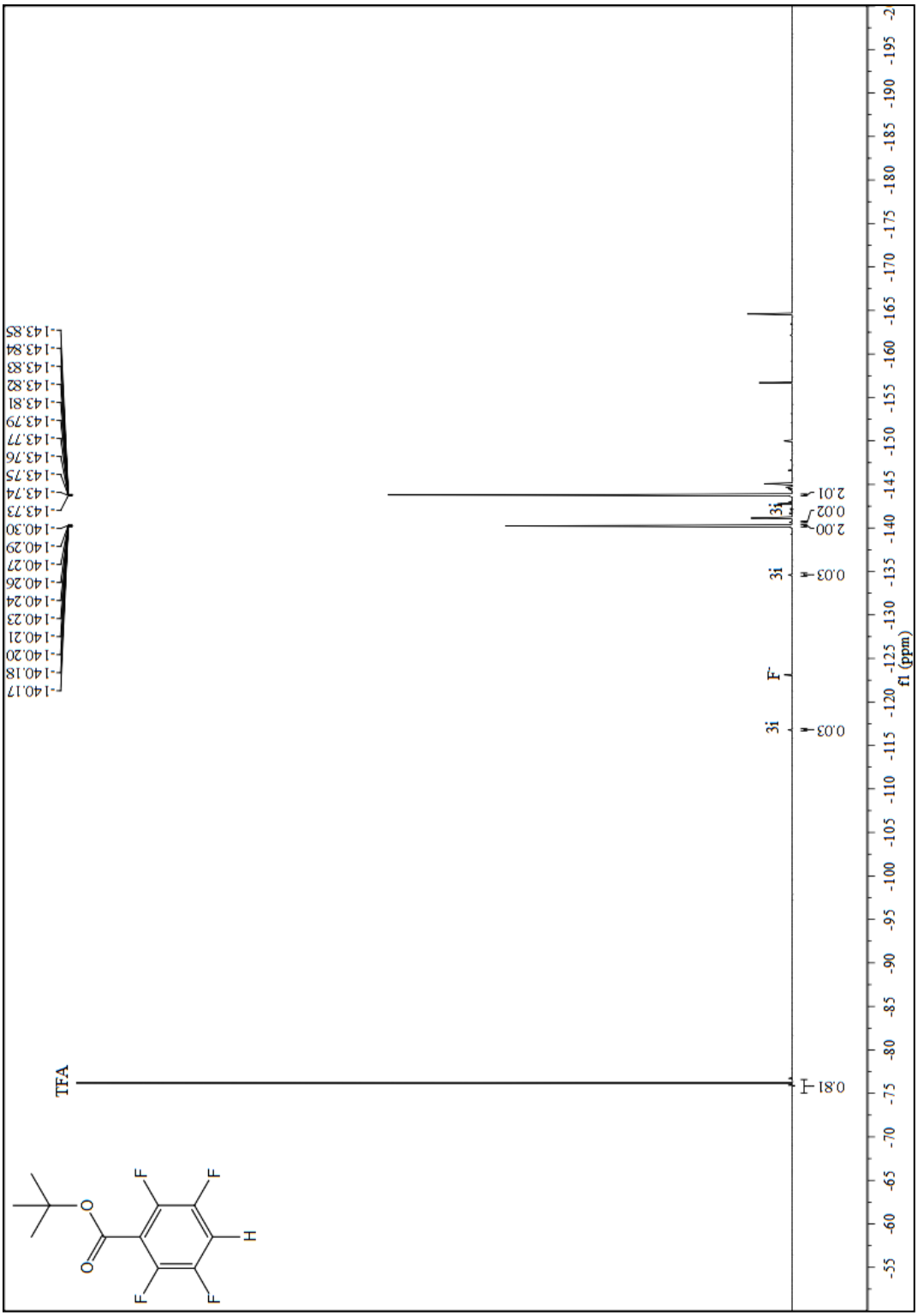
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7f (*N*-(2,3,6-trifluoro-4-(trifluoromethyl)phenyl)acetamide)



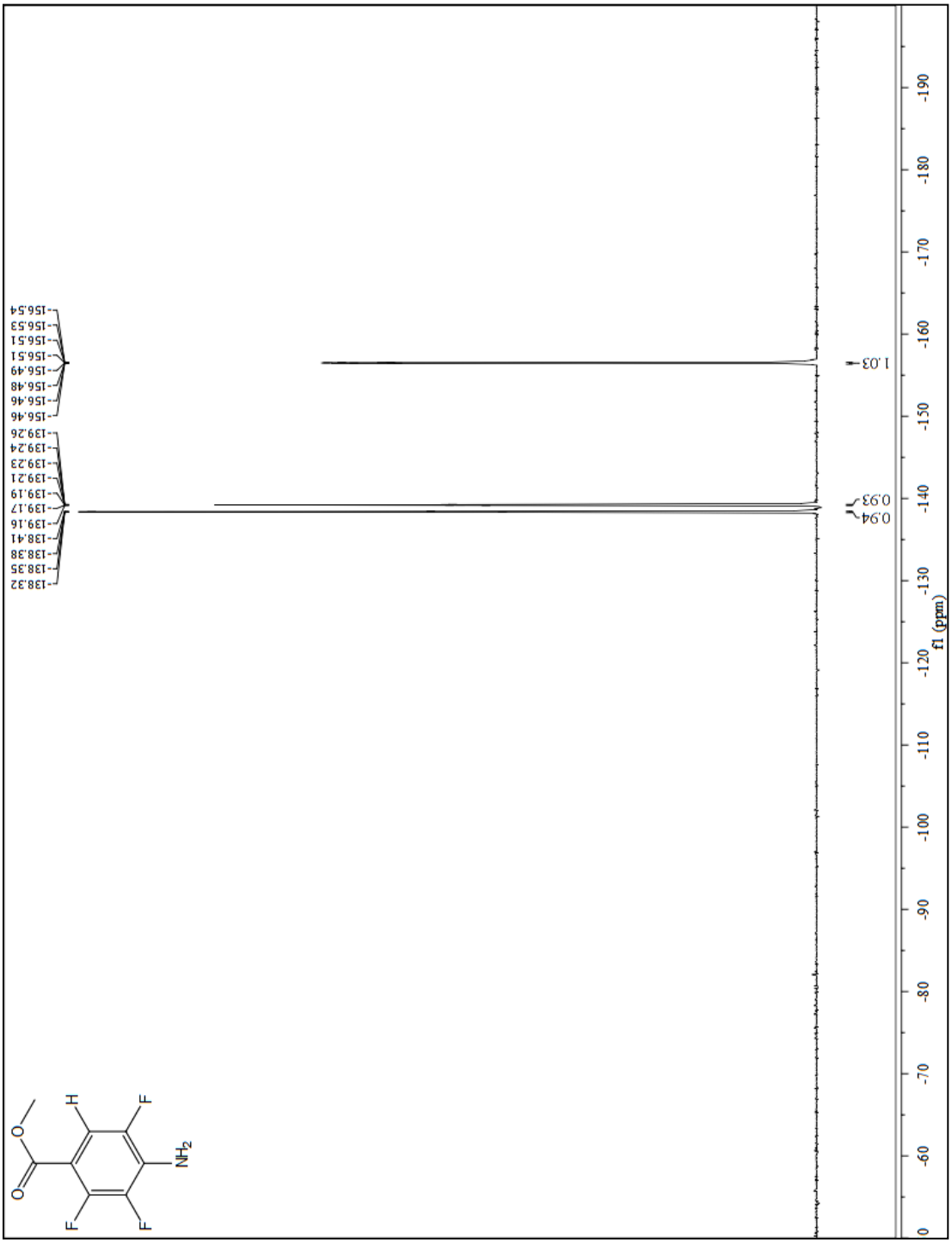
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7f (*N*-(2,3,6-trifluoro-4-(trifluoromethyl)phenyl)acetamide)



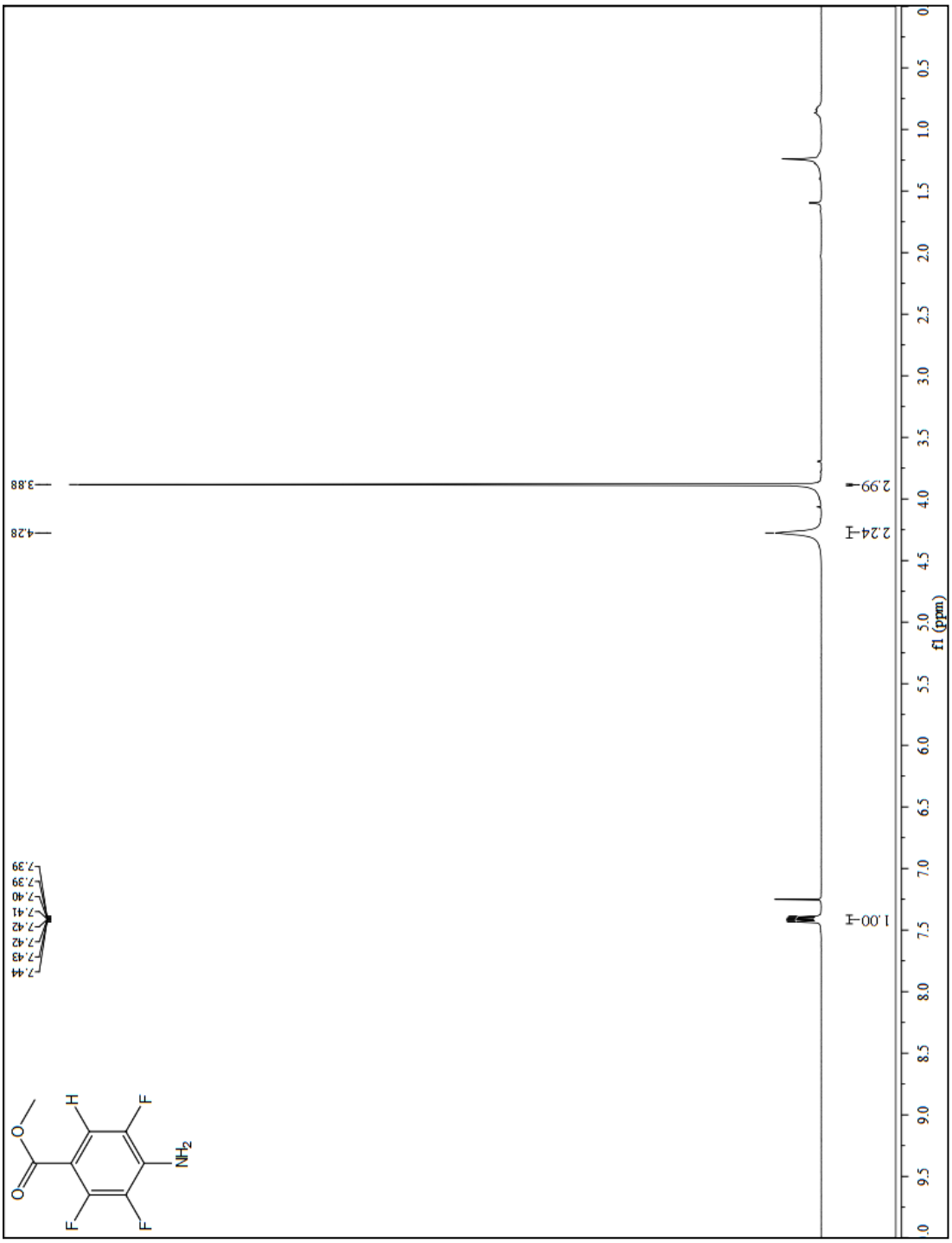
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7g (tert-butyl 2,3,5,6-tetrafluorobenzoate)



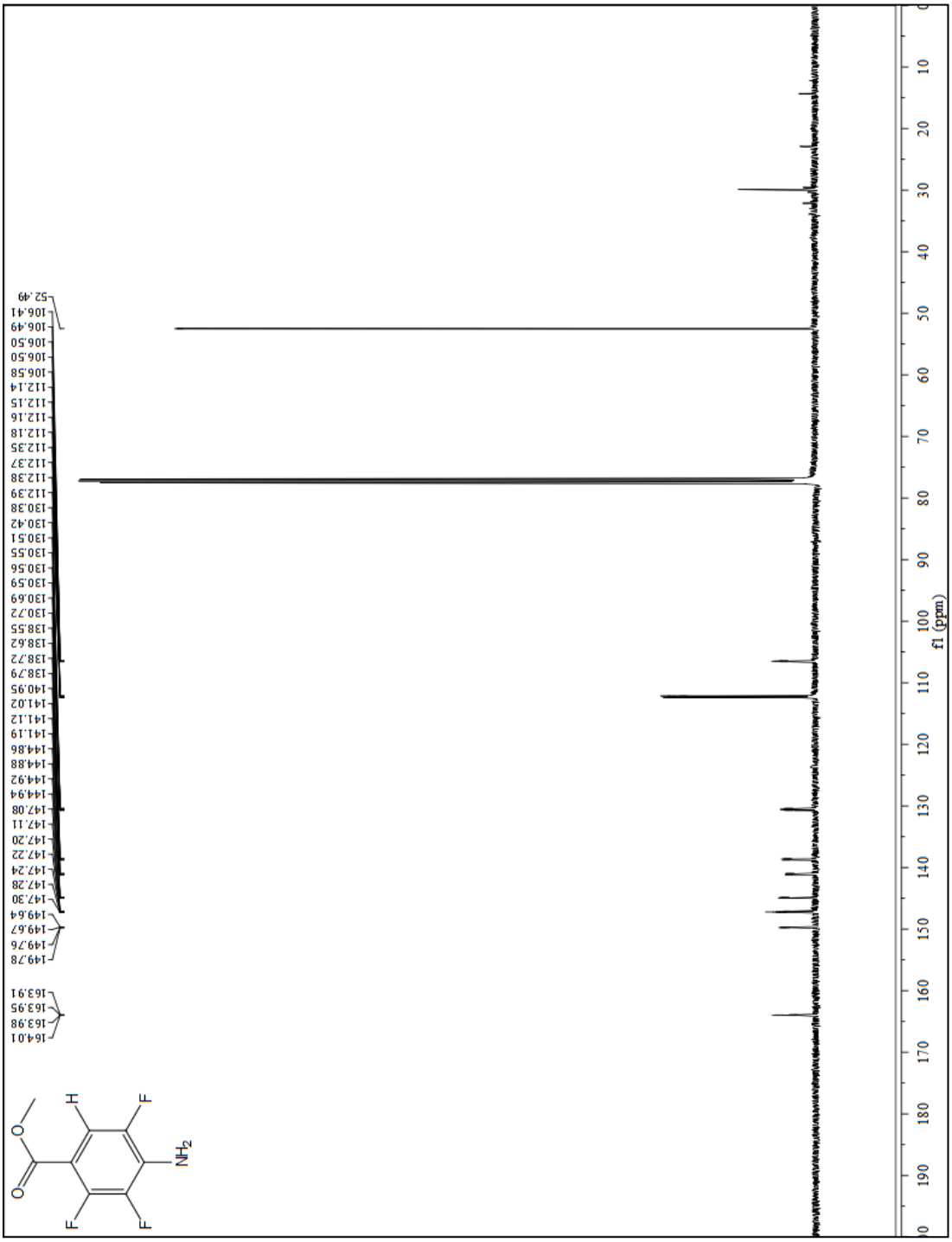
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7h (methyl 4-amino-2,3,5-trifluorobenzoate)



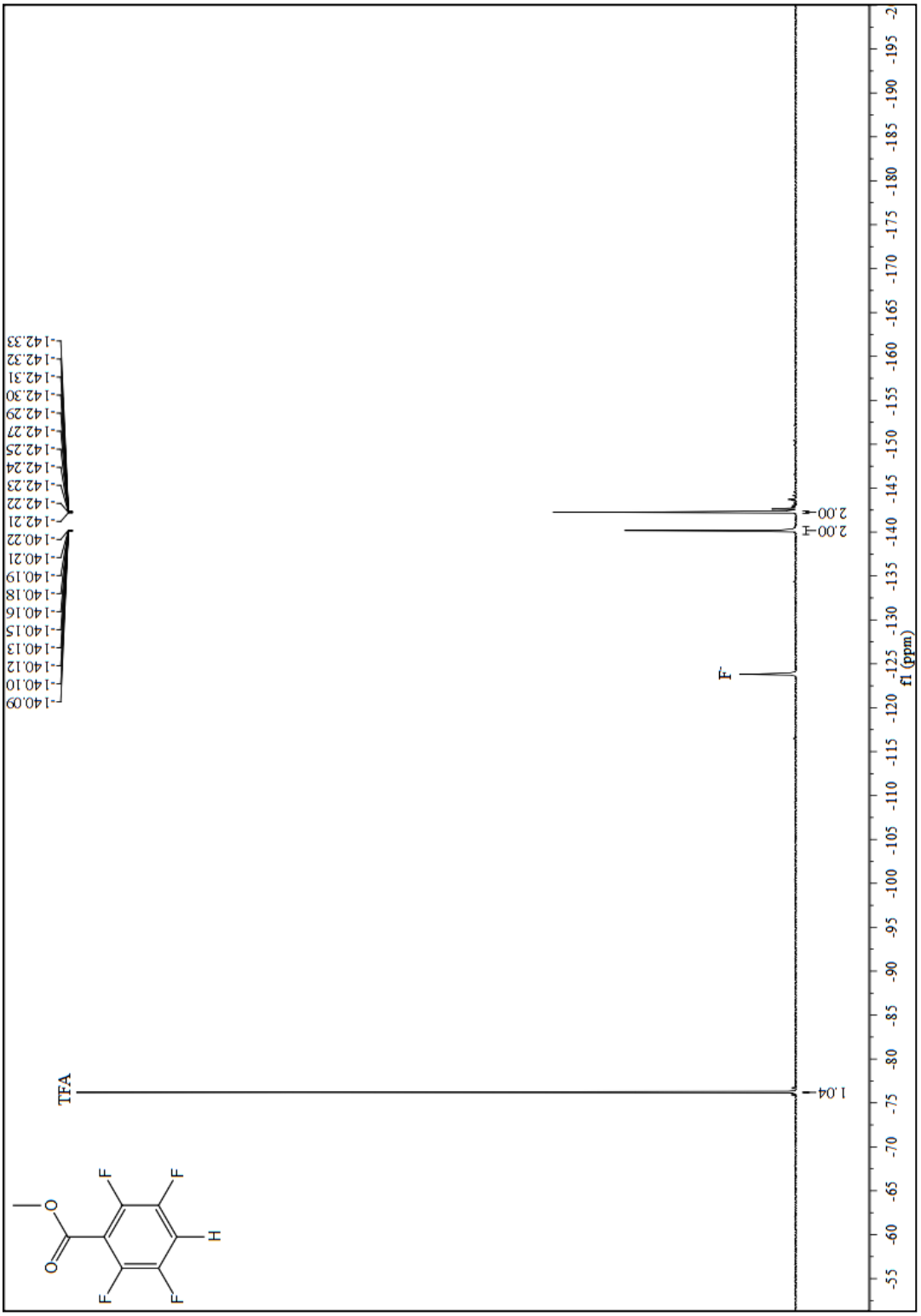
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7h (methyl 4-amino-2,3,5-trifluorobenzoate)



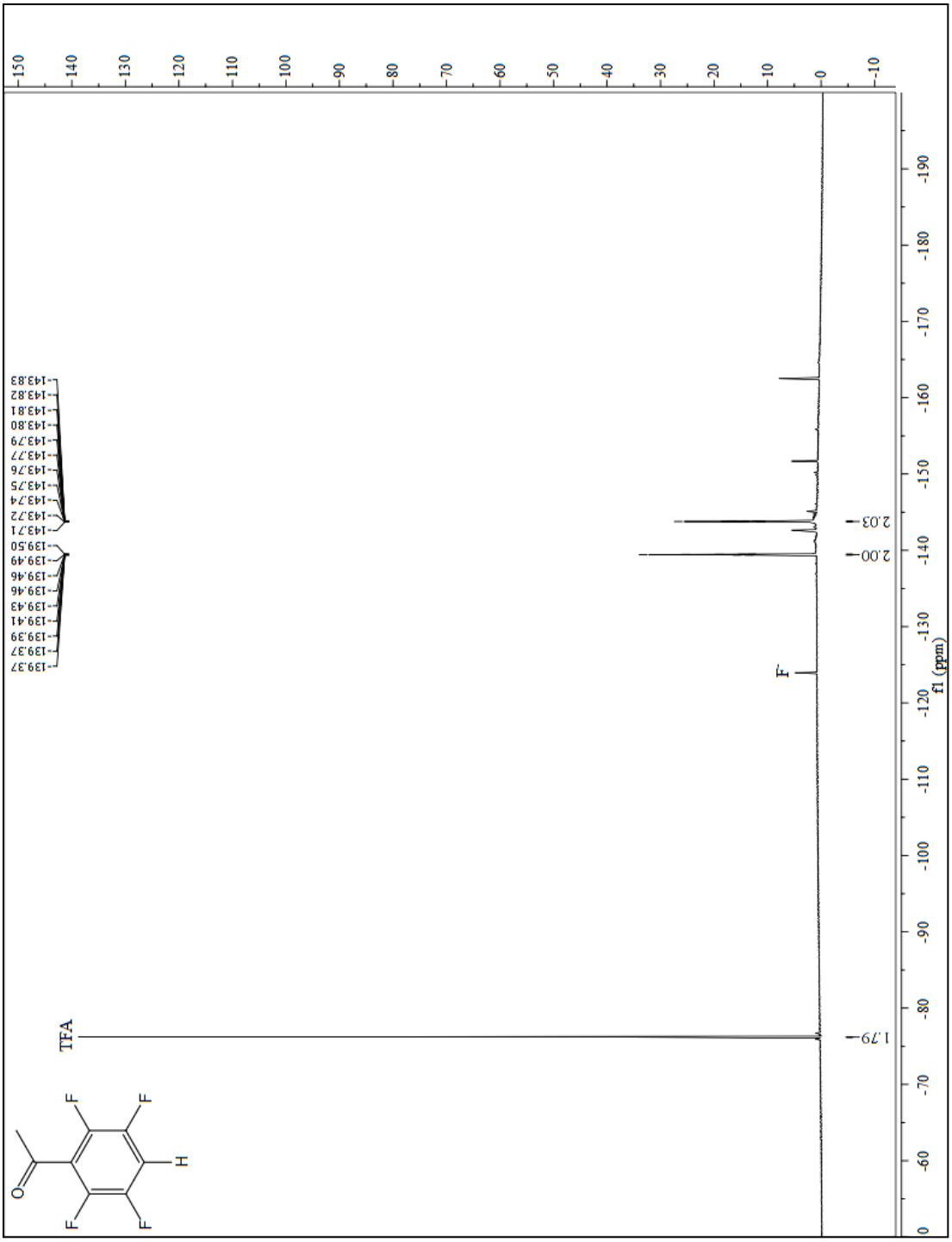
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7h (methyl 4-amino-2,3,5-trifluorobenzoate)



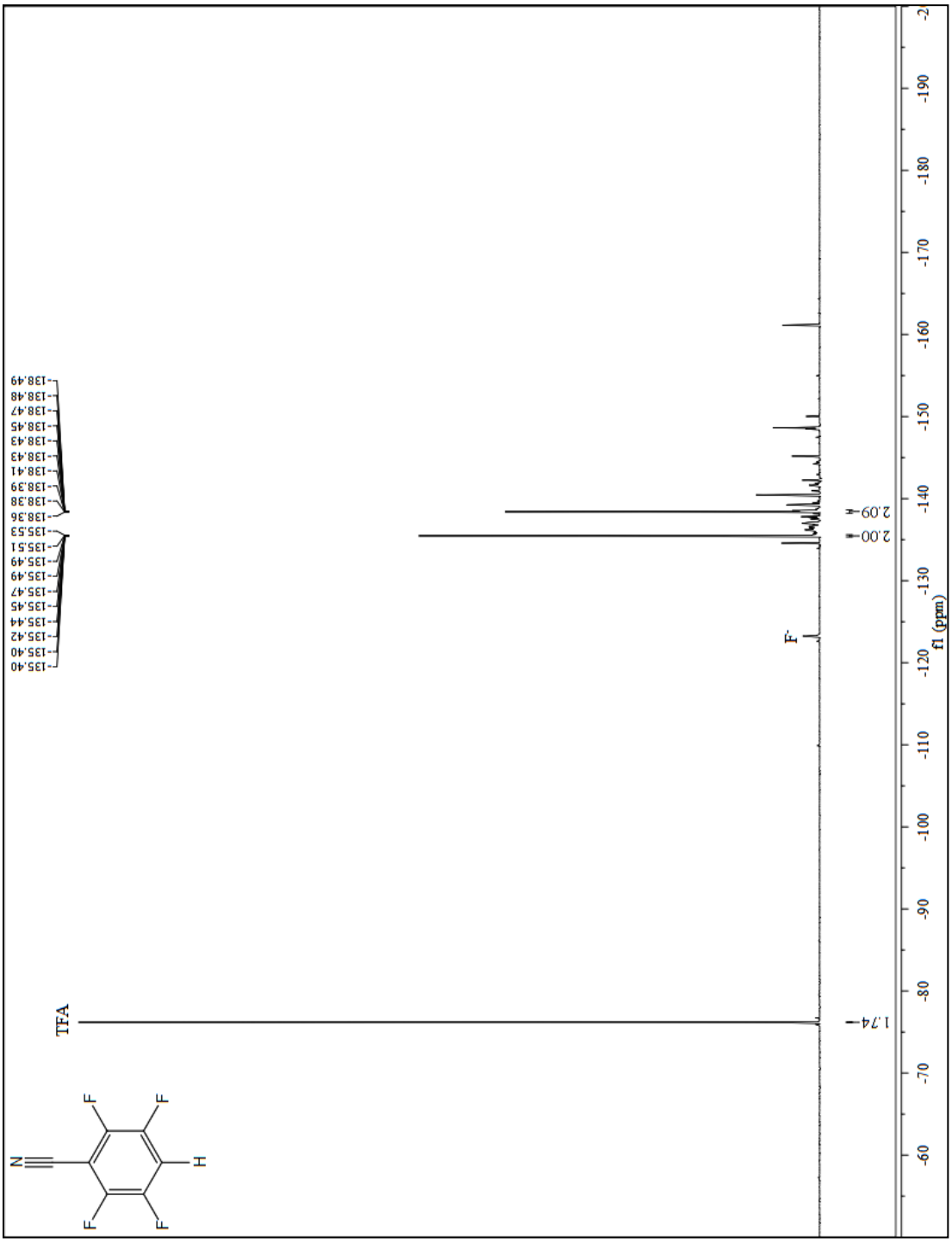
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7i (methyl 2,3,5,6-tetrafluorobenzoate)



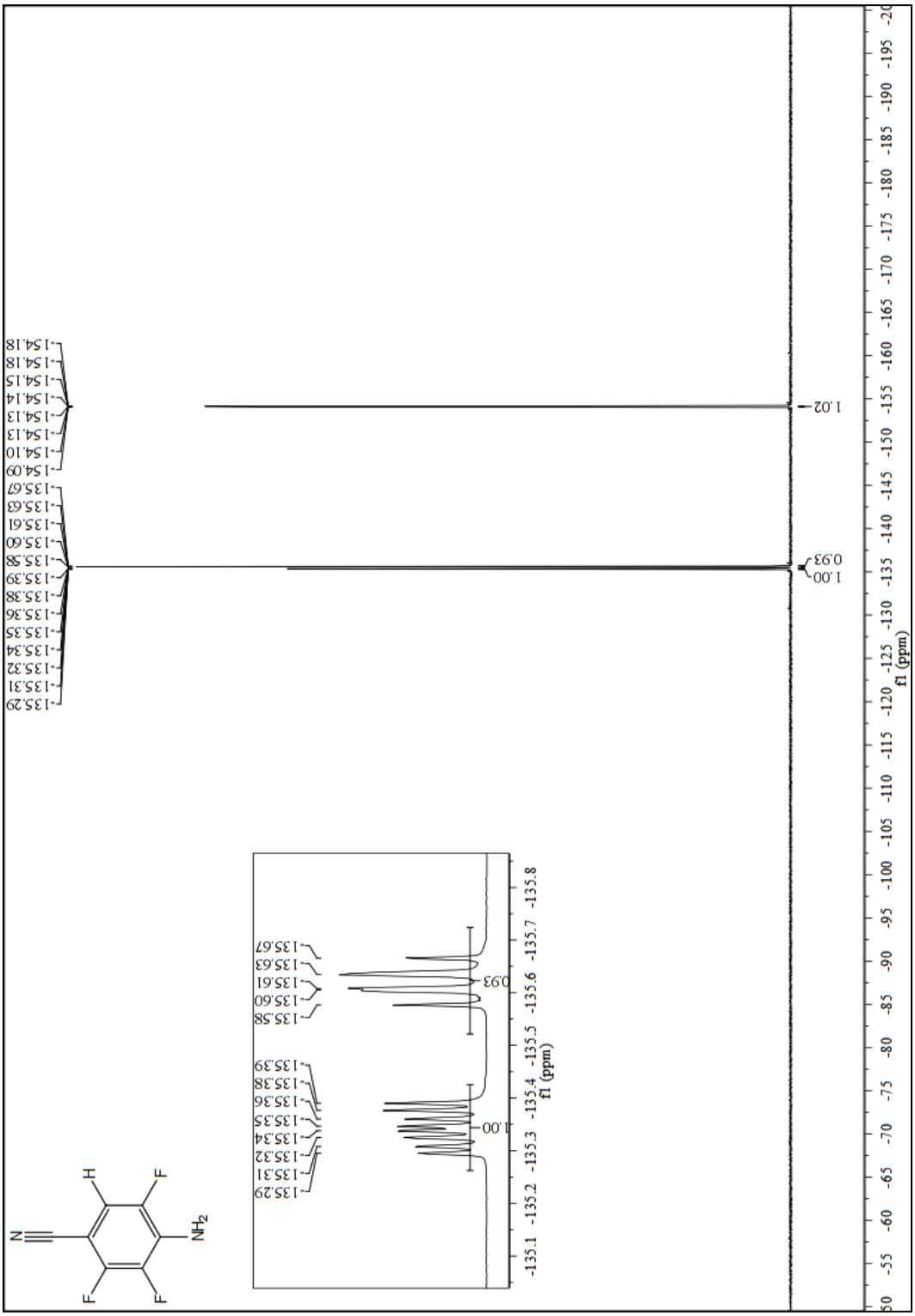
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7j (1-(2,3,5,6-tetrafluorophenyl)ethan-1-one)



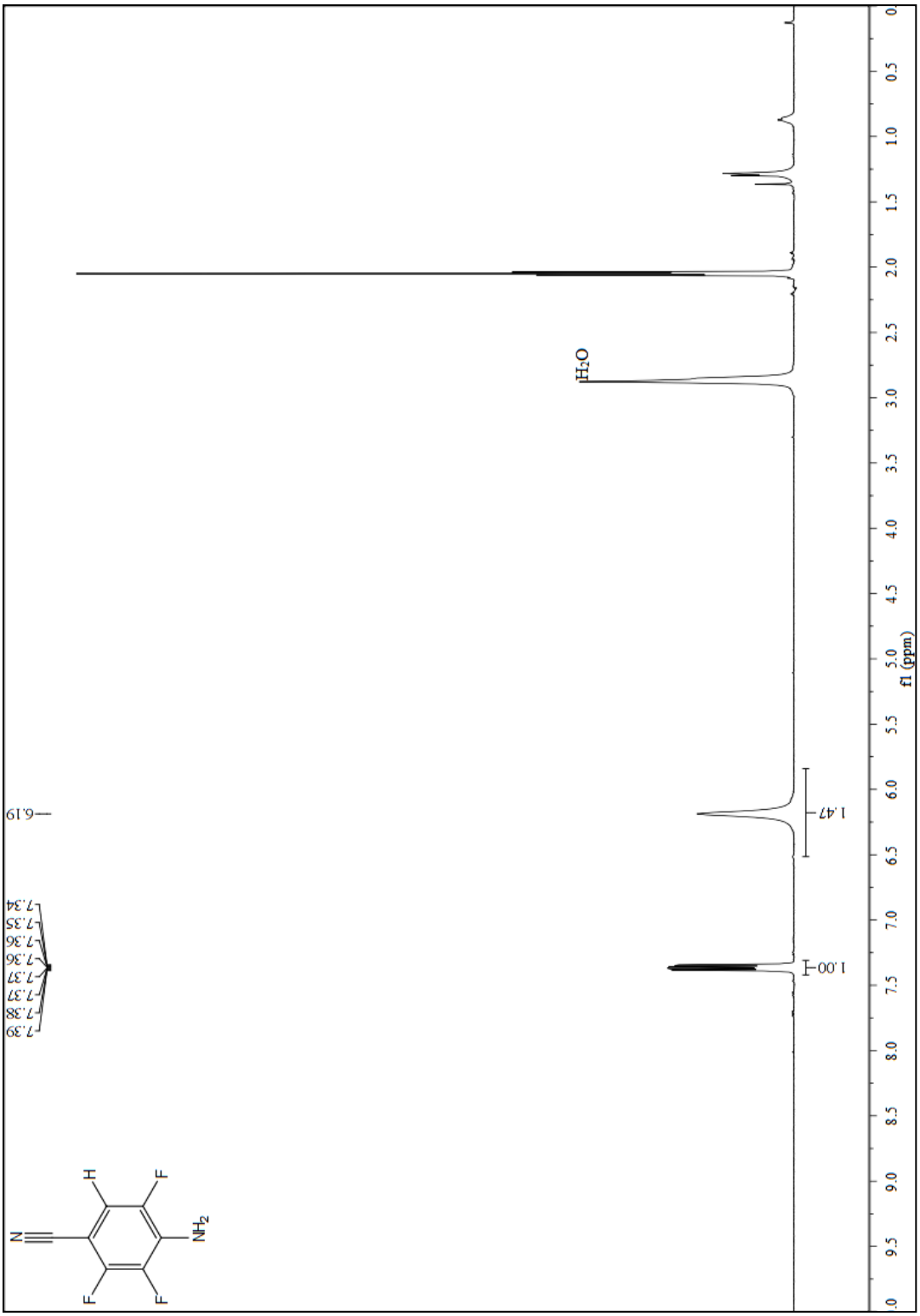
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7k (2,3,5,6-tetrafluorobenzonitrile)



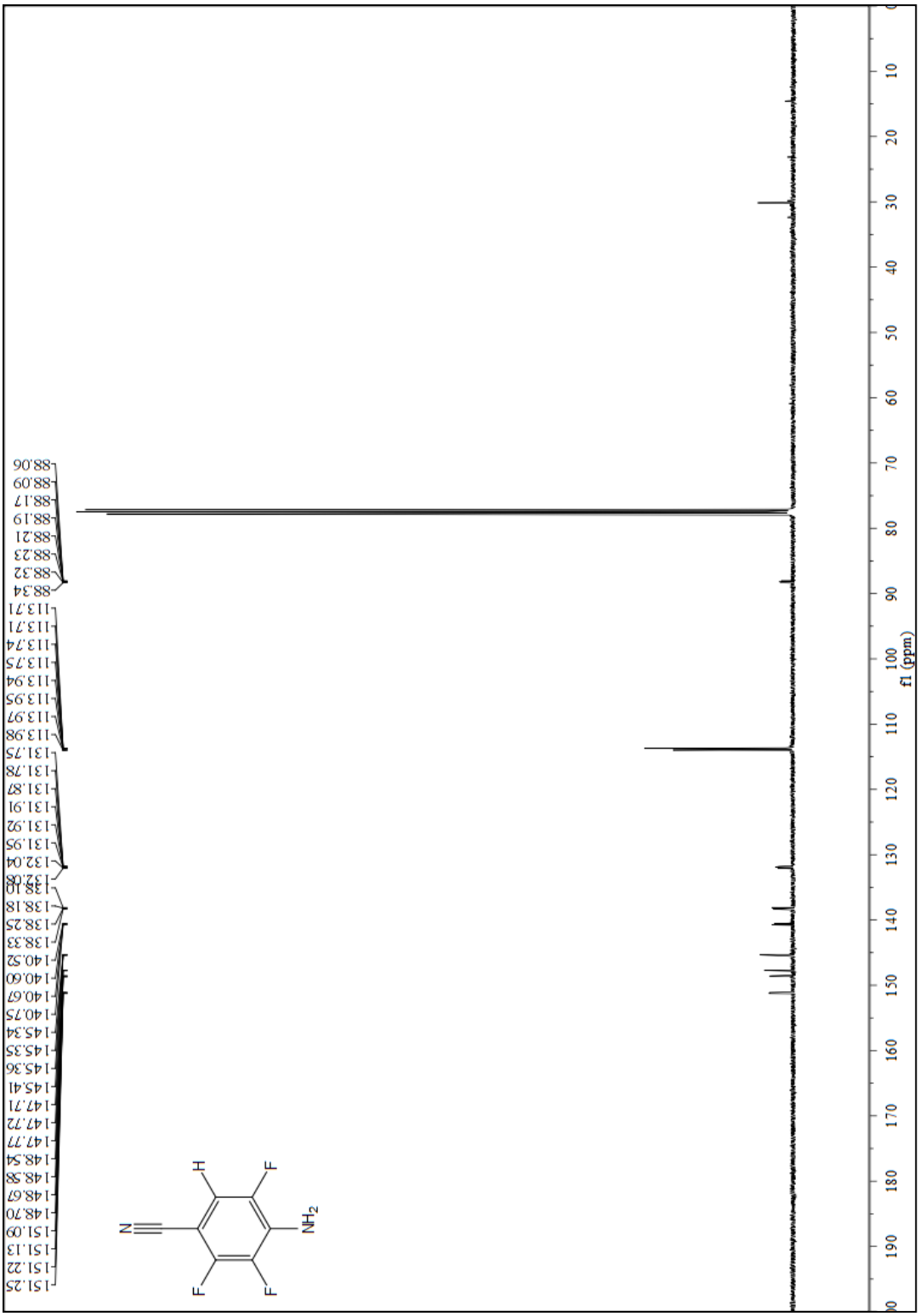
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7l (4-amino-2,3,5-trifluorobenzonitrile)



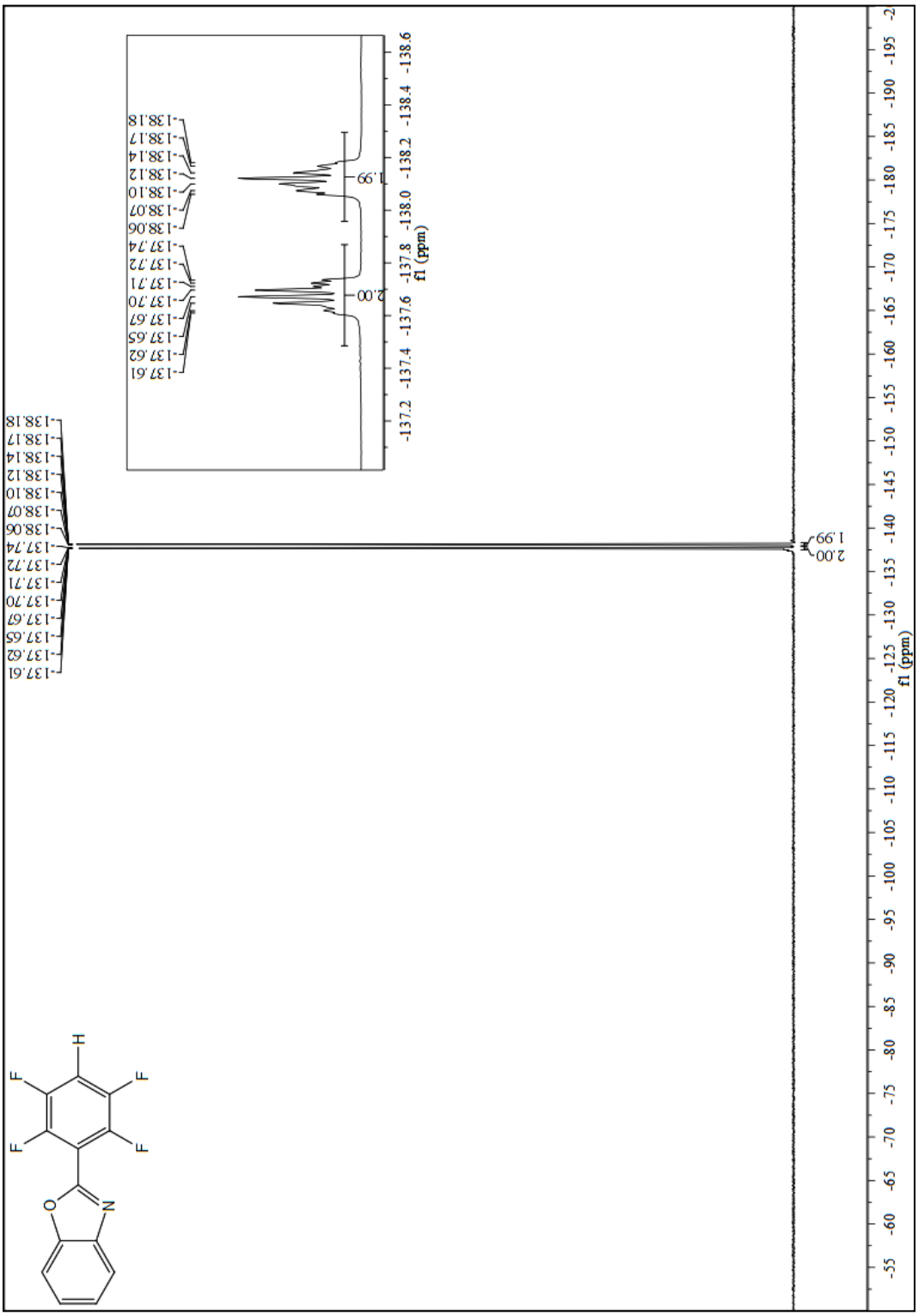
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7l (4-amino-2,3,5-trifluorobenzonitrile)



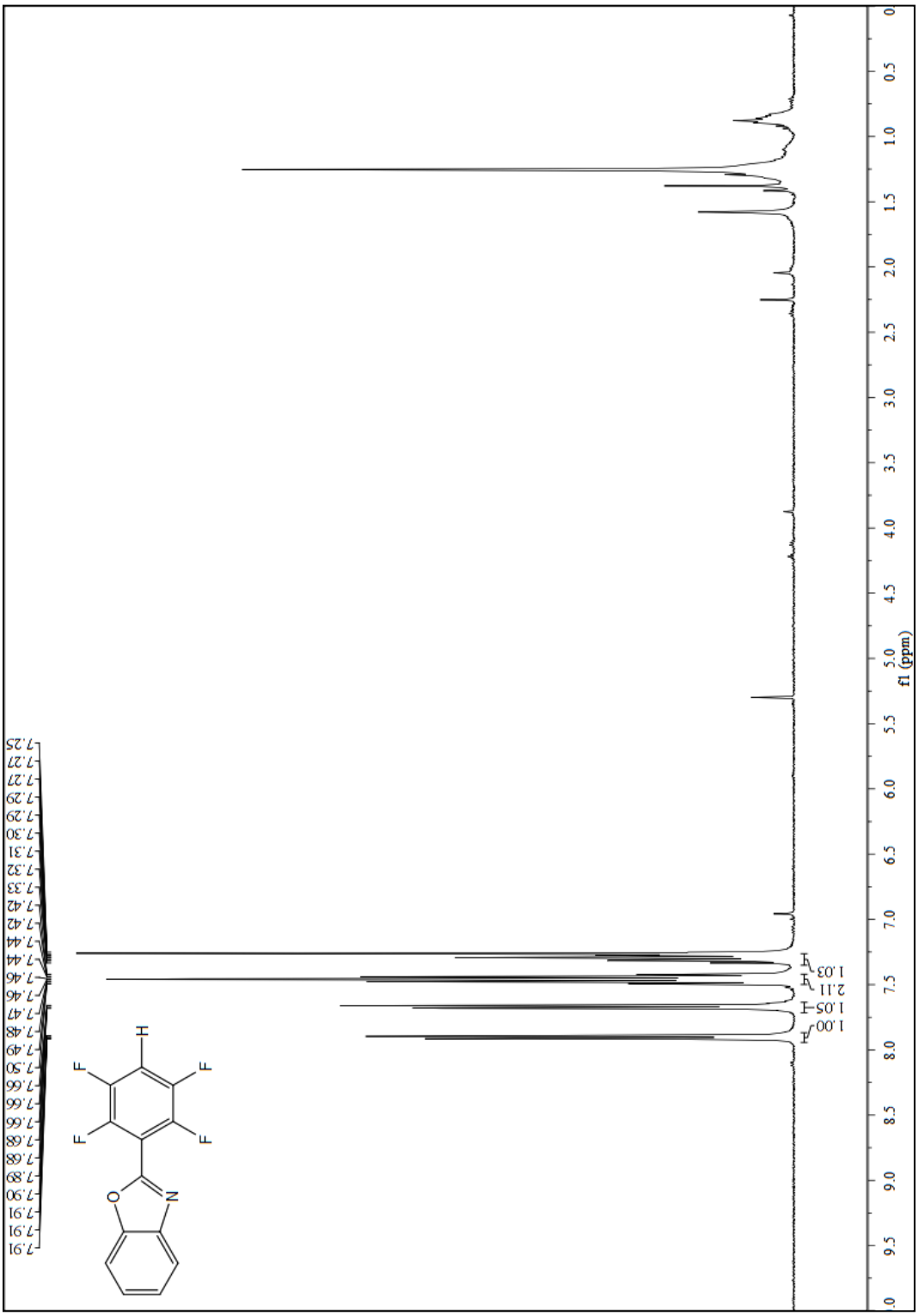
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7l (4-amino-2,3,5-trifluorobenzonitrile)



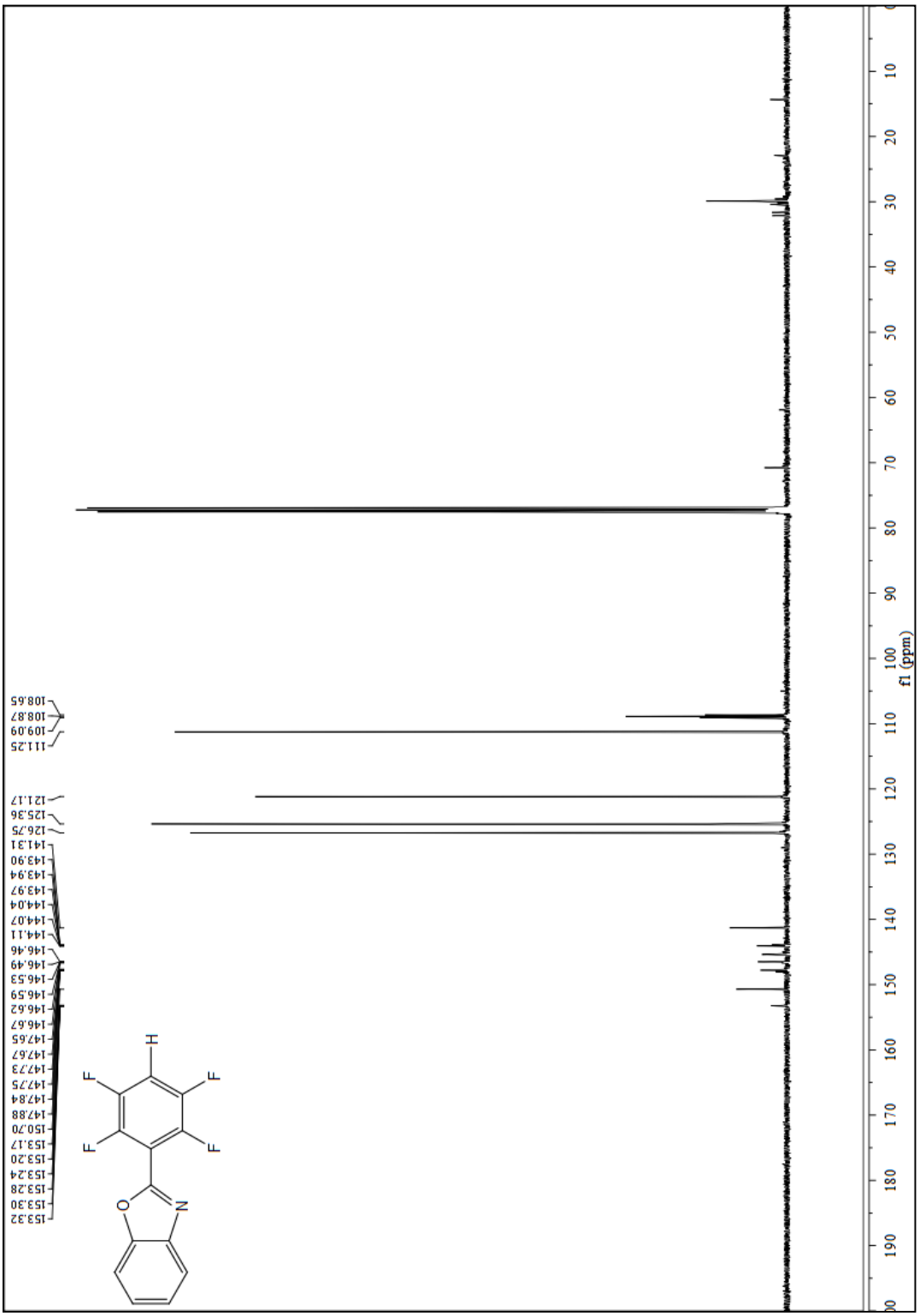
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7m (2-(2,3,5,6-tetrafluorophenyl)benzo[d]oxazole)



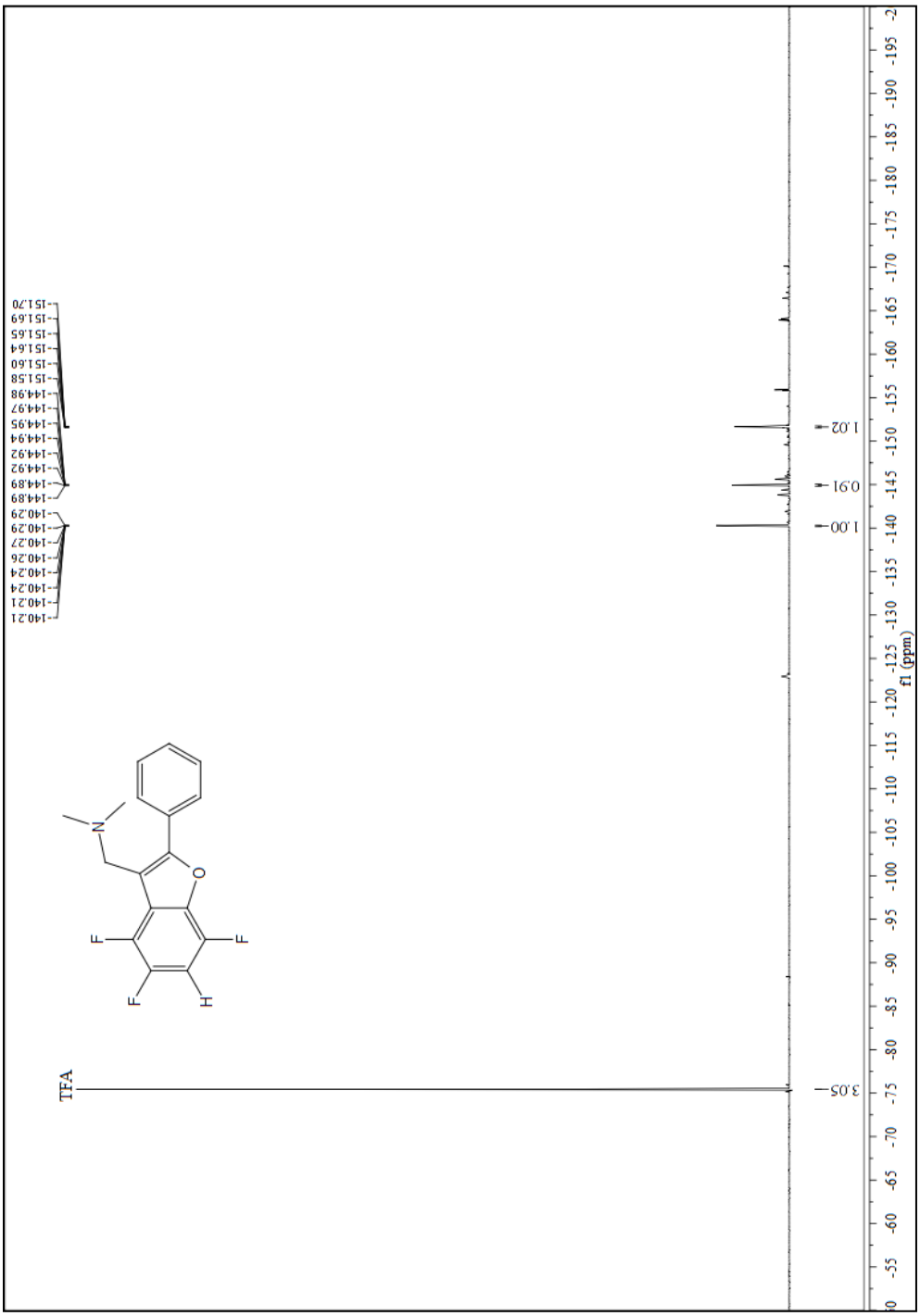
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7m (2-(2,3,5,6-tetrafluorophenyl)benzo[d]oxazole)



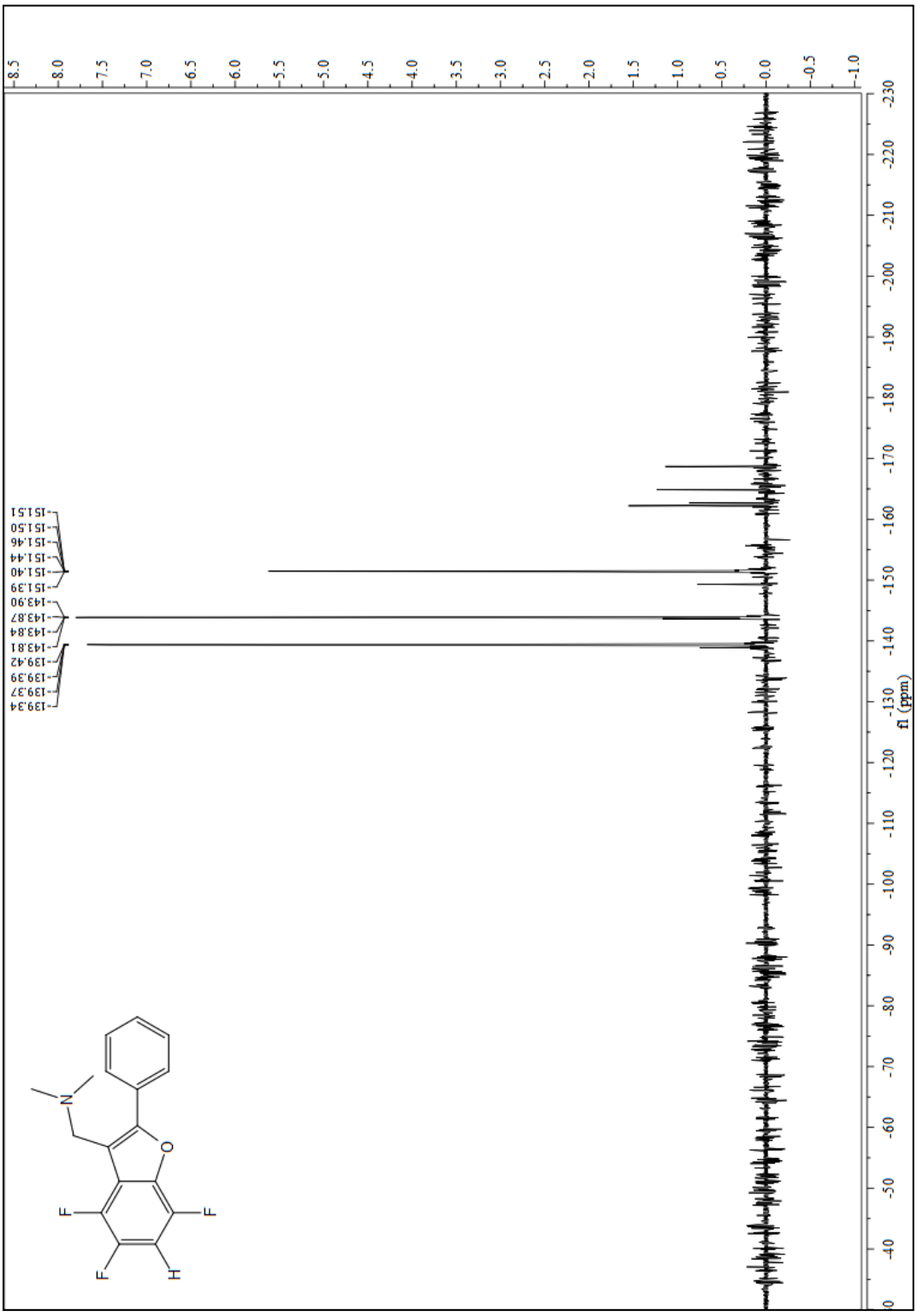
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7m (2-(2,3,5,6-tetrafluorophenyl)benzo[d]oxazole



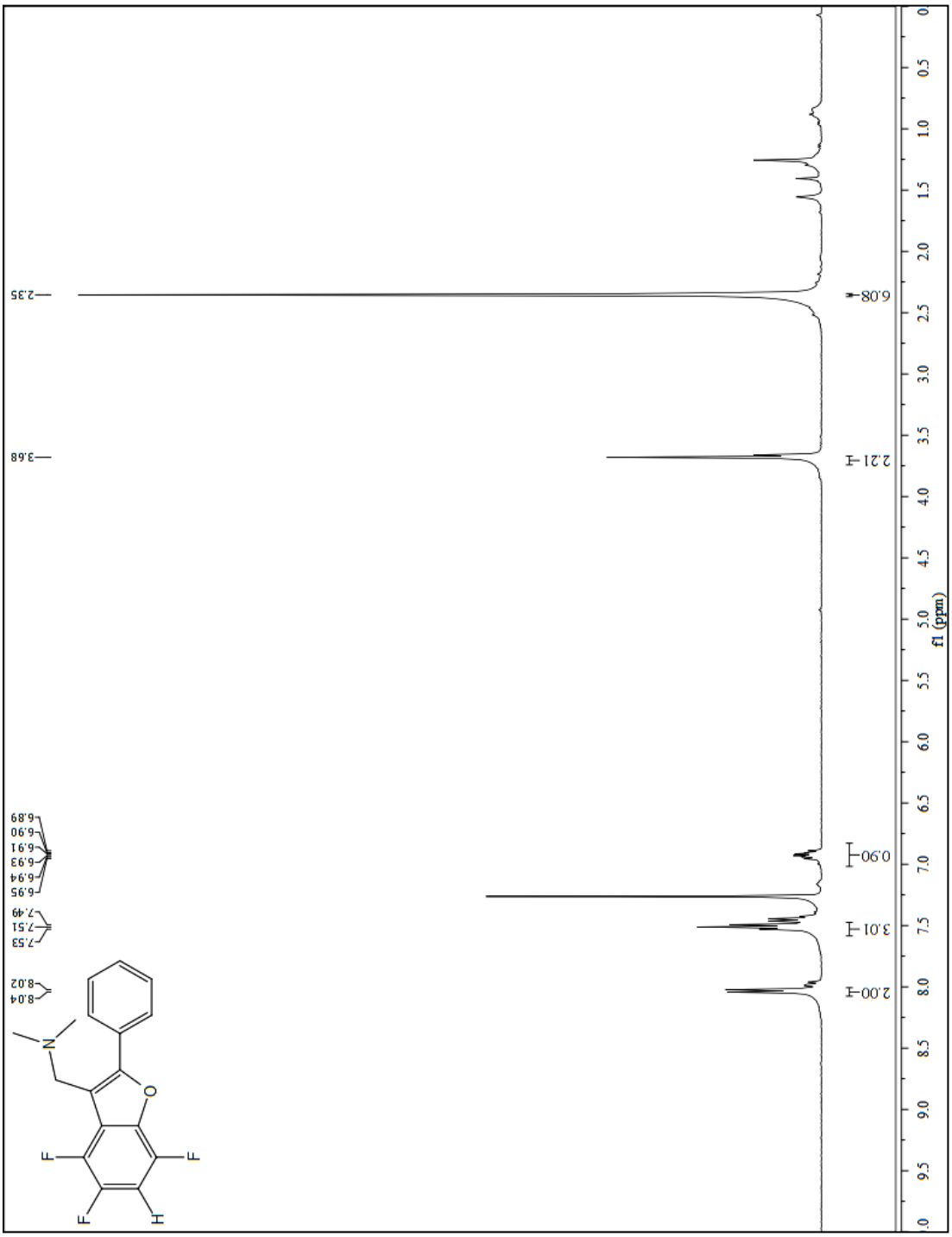
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7n (*N*,*N*-dimethyl-1-(4,5,7-trifluoro-2-phenylbenzofuran-3-yl)methanamine) ^{19}F NMR yield



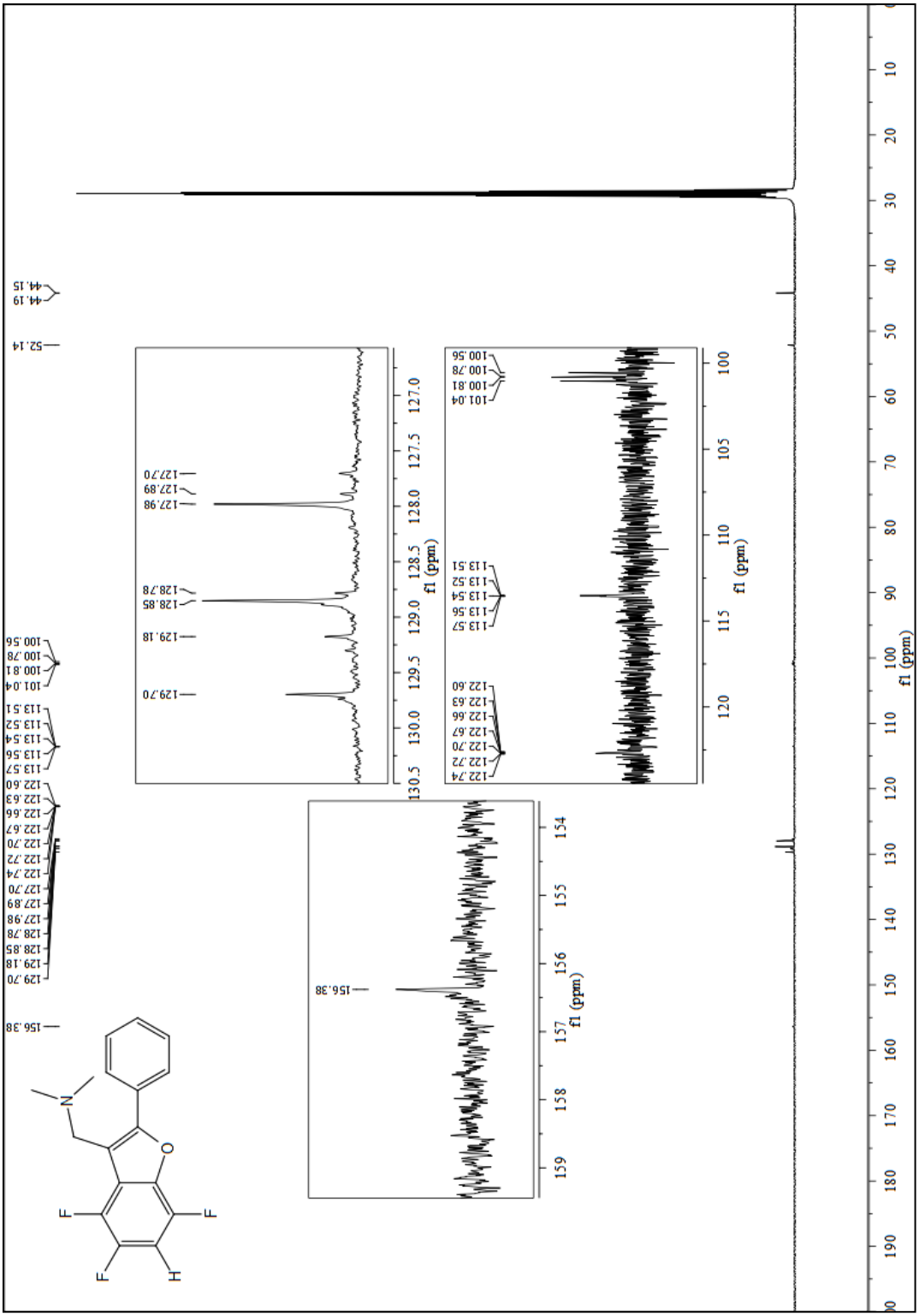
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7n (*N*,*N*-dimethyl-1-(4,5,7-trifluoro-2-phenylbenzofuran-3-yl)methanamine)



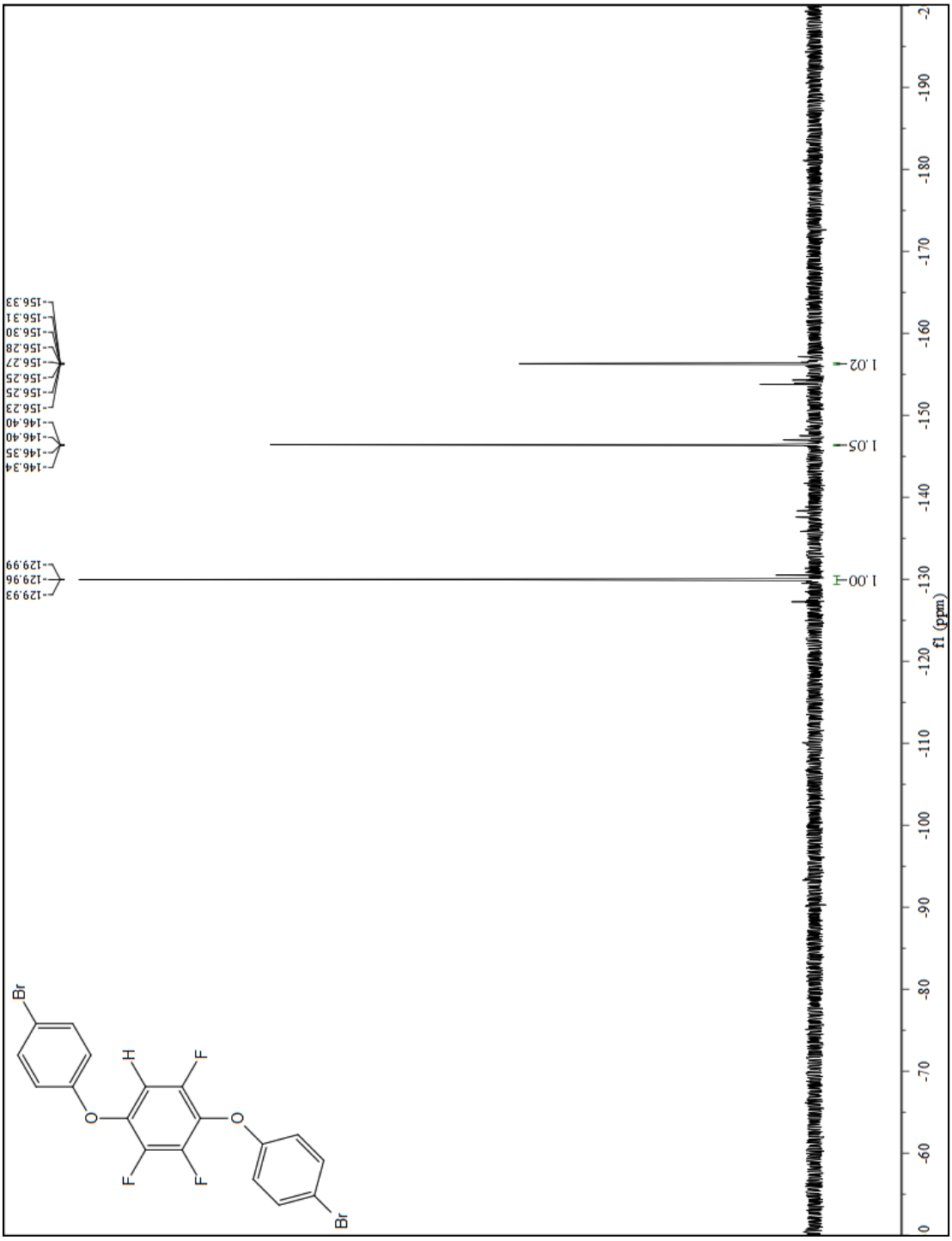
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7n (*N,N*-dimethyl-1-(4,5,7-trifluoro-2-phenylbenzofuran-3-yl)methanamine)



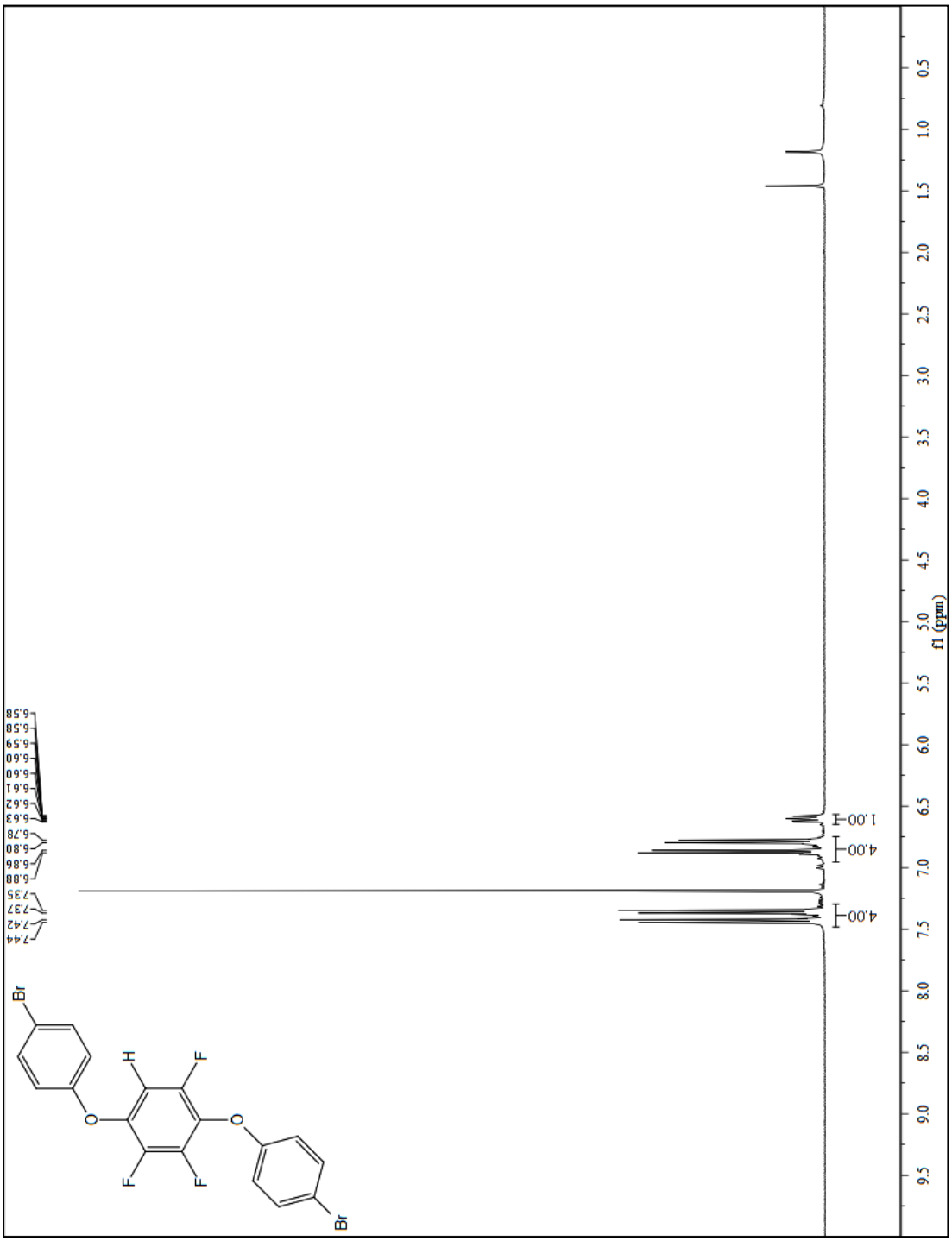
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7n (*N*,*N*-dimethyl-1-(4,5,7-trifluoro-2-phenylbenzofuran-3-yl)methanamine)



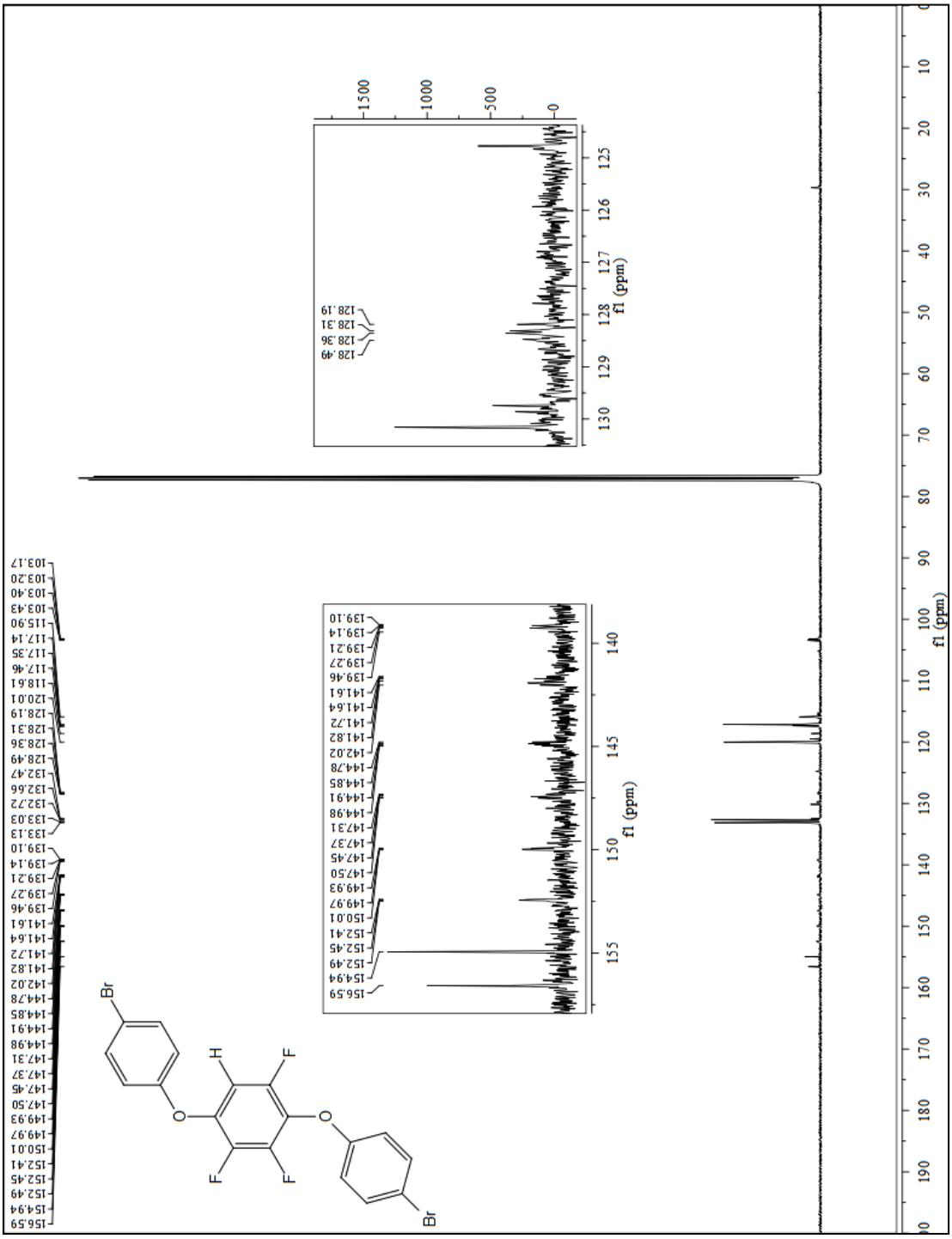
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7o (4,4'-((2,3,5-trifluoro-1,4-phenylene)bis(oxy))bis(bromobenzene))



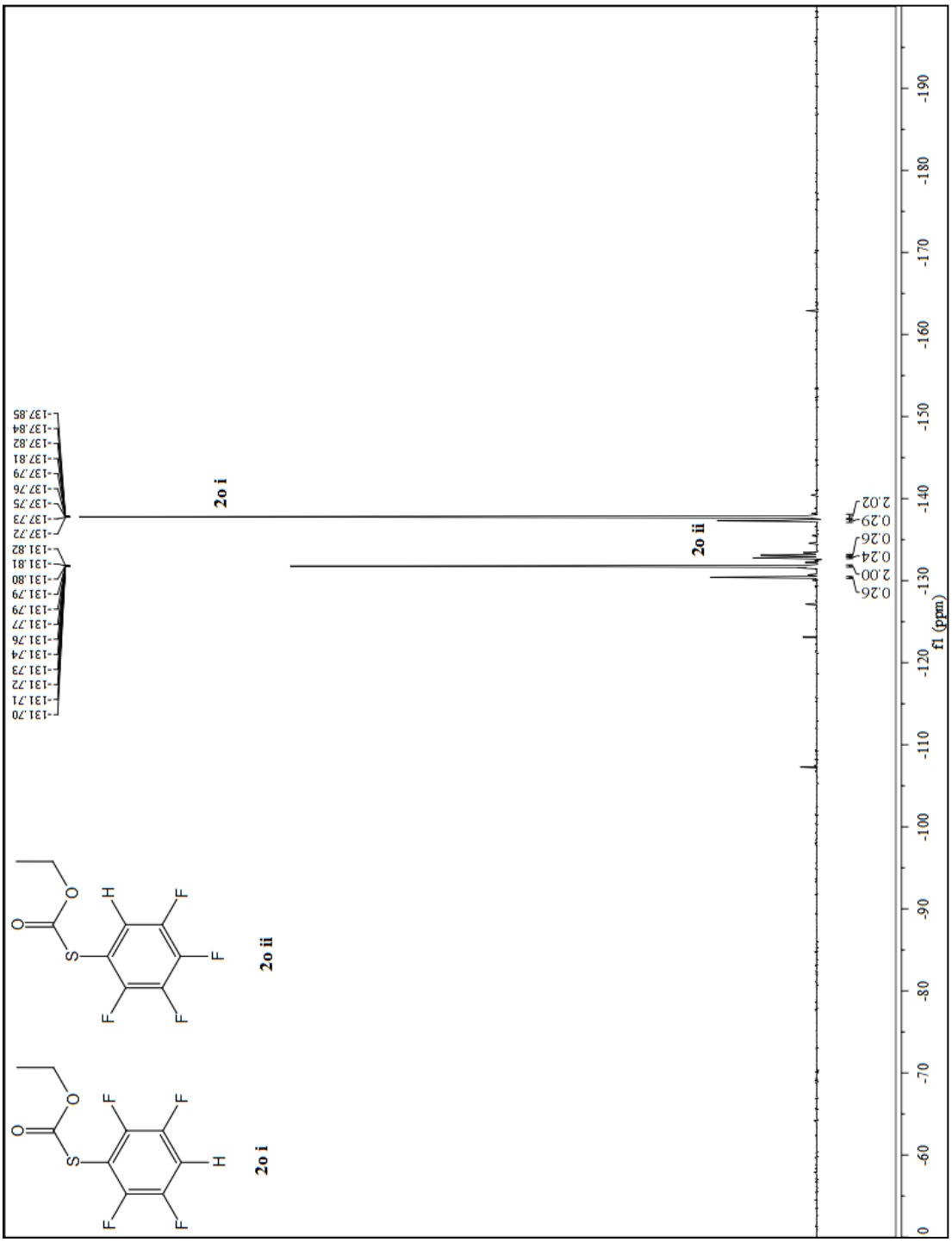
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7o (4,4'-((2,3,5-trifluoro-1,4-phenylene)bis(oxy))bis(bromobenzene))



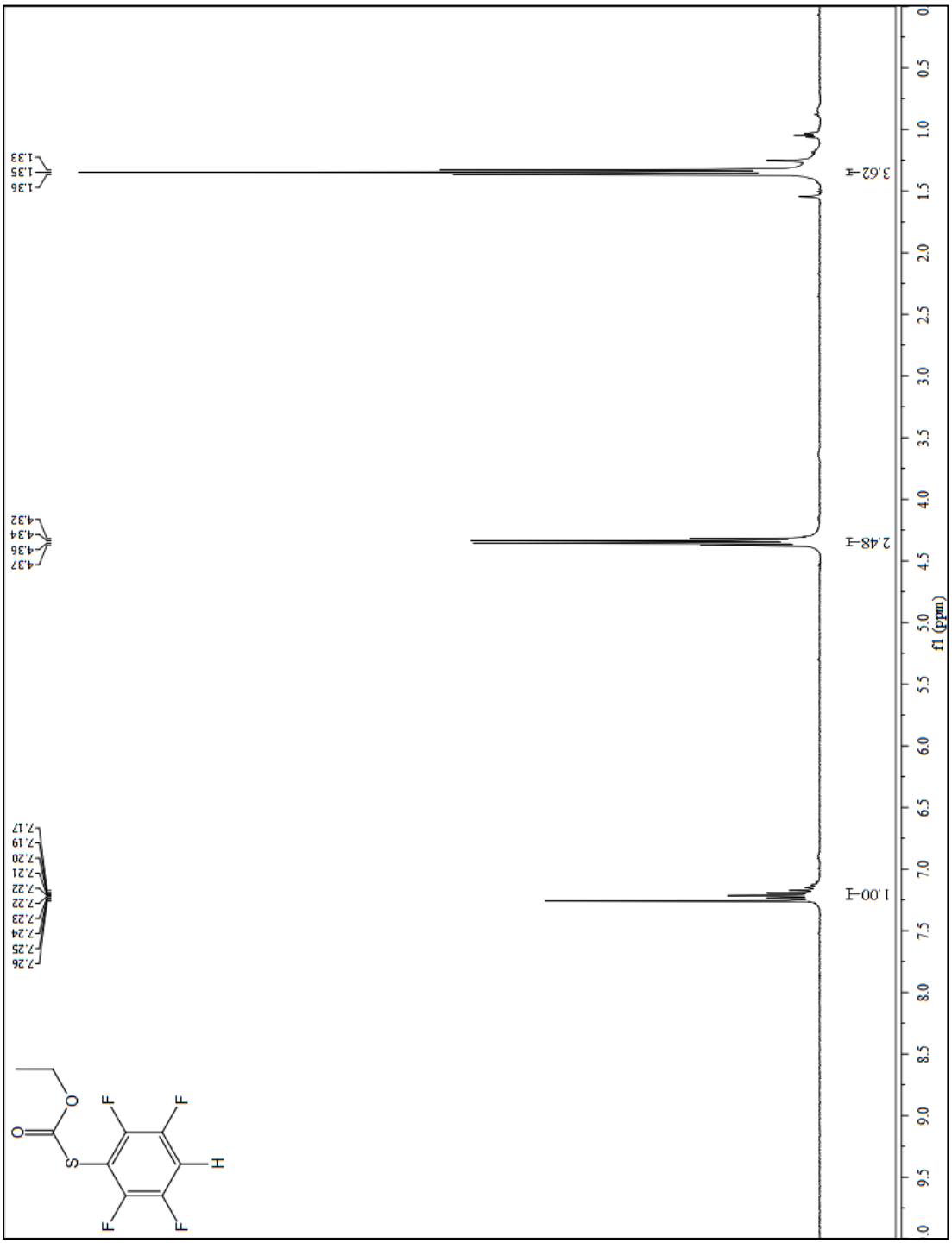
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7o (4,4'-((2,3,5-trifluoro-1,4-phenylene)bis(oxy))bis(bromobenzene))



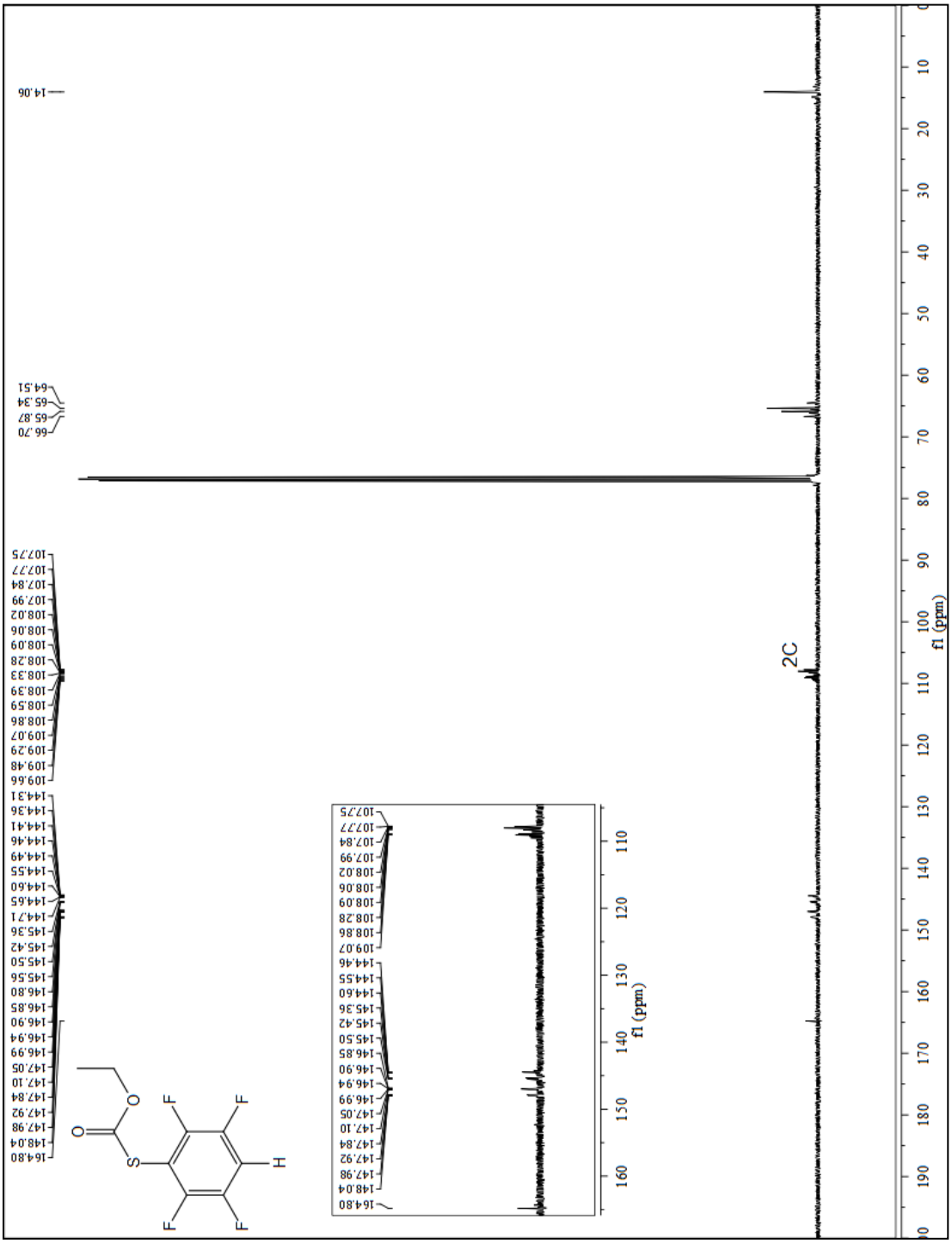
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7p (*O*-ethyl *S*-(2,3,5,6-tetrafluorophenyl) carbonothioate)



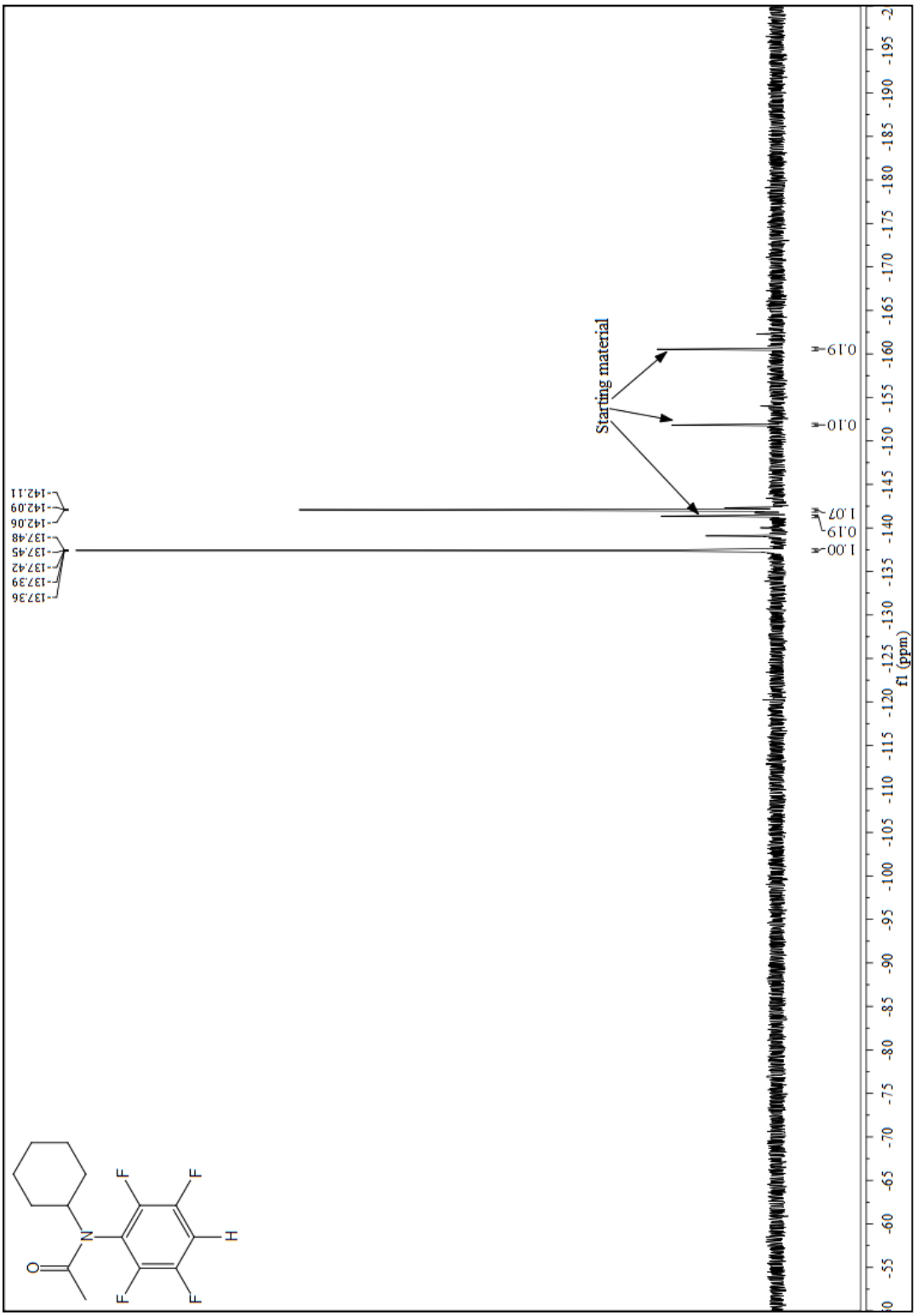
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7p (*O*-ethyl *S*-(2,3,5,6-tetrafluorophenyl) carbonothioate)



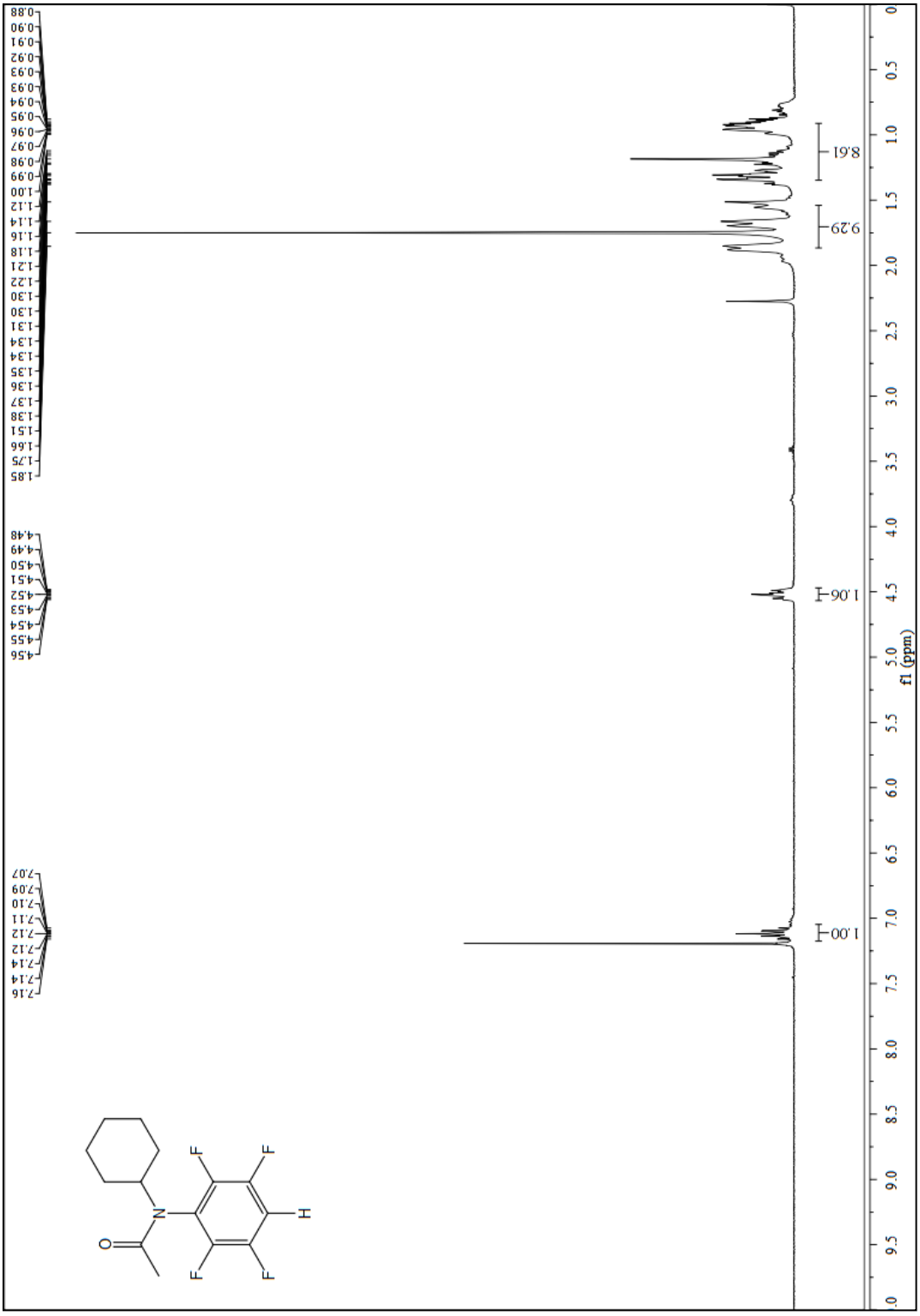
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7p (*O*-ethyl *S*-(2,3,5,6-tetrafluorophenyl) carbonothioate)



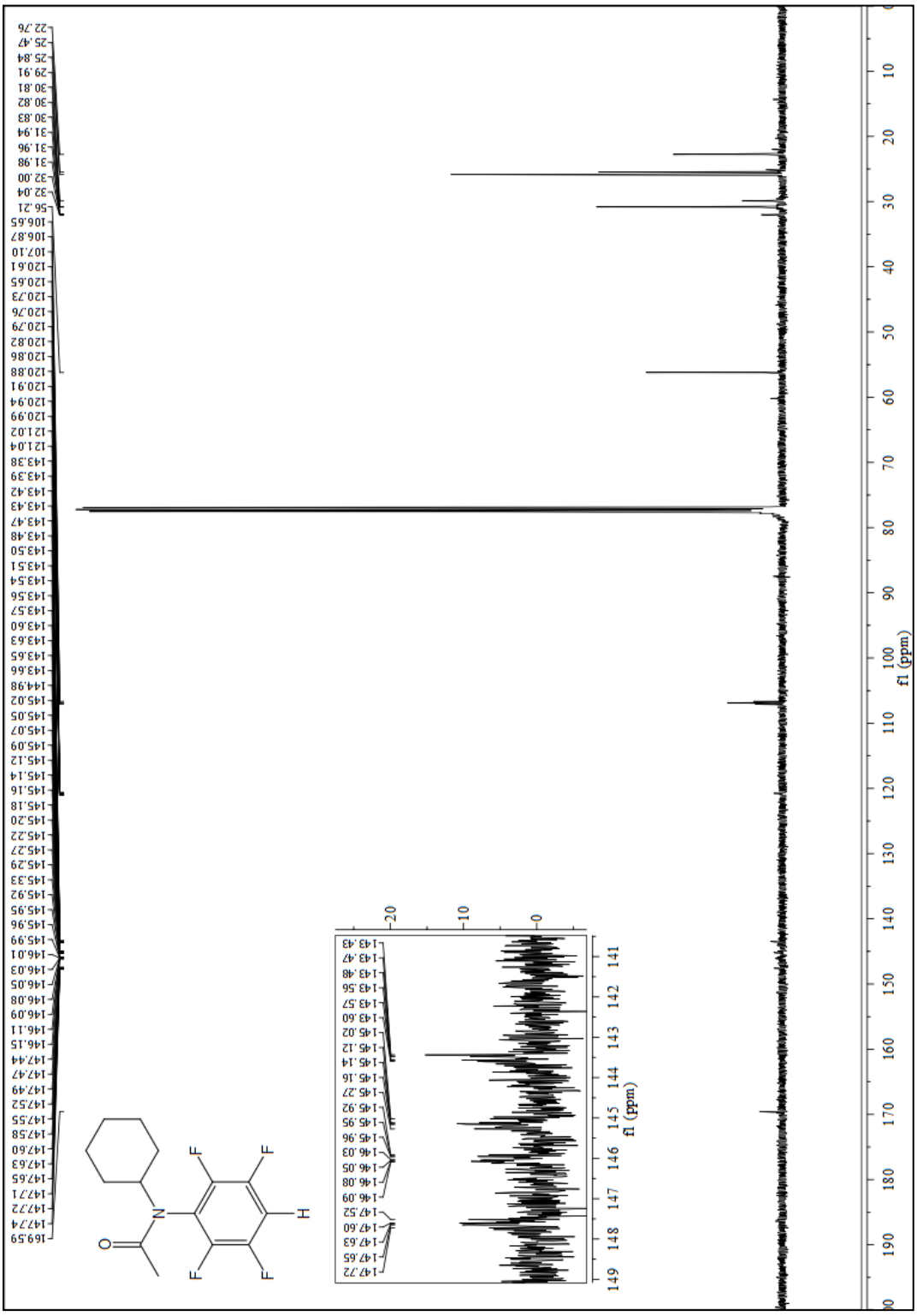
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7q (*N*-cyclohexyl-N-(2,3,5,6-tetrafluorophenyl)acetamide)



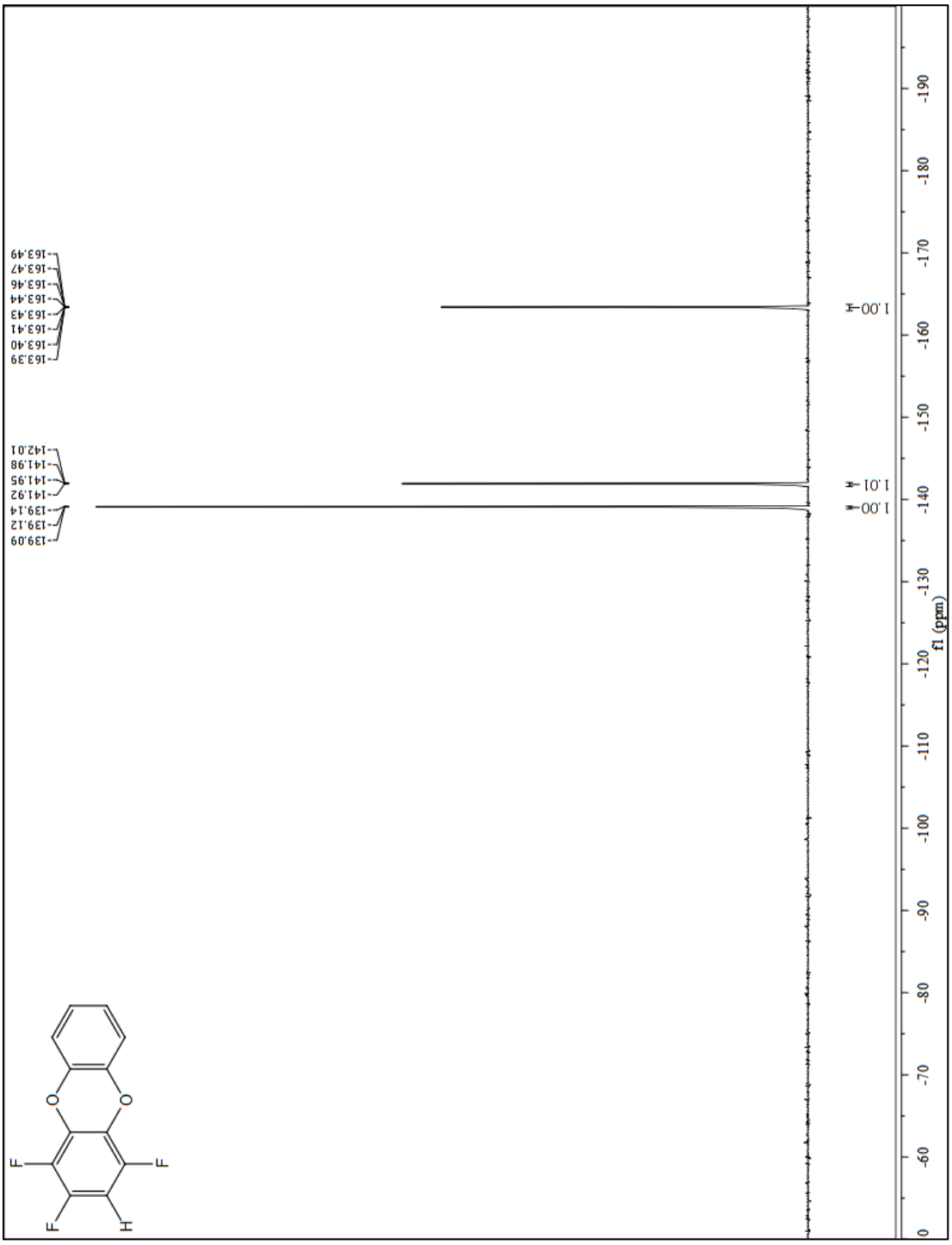
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7q (*N*-cyclohexyl-N-(2,3,5,6-tetrafluorophenyl)acetamide)



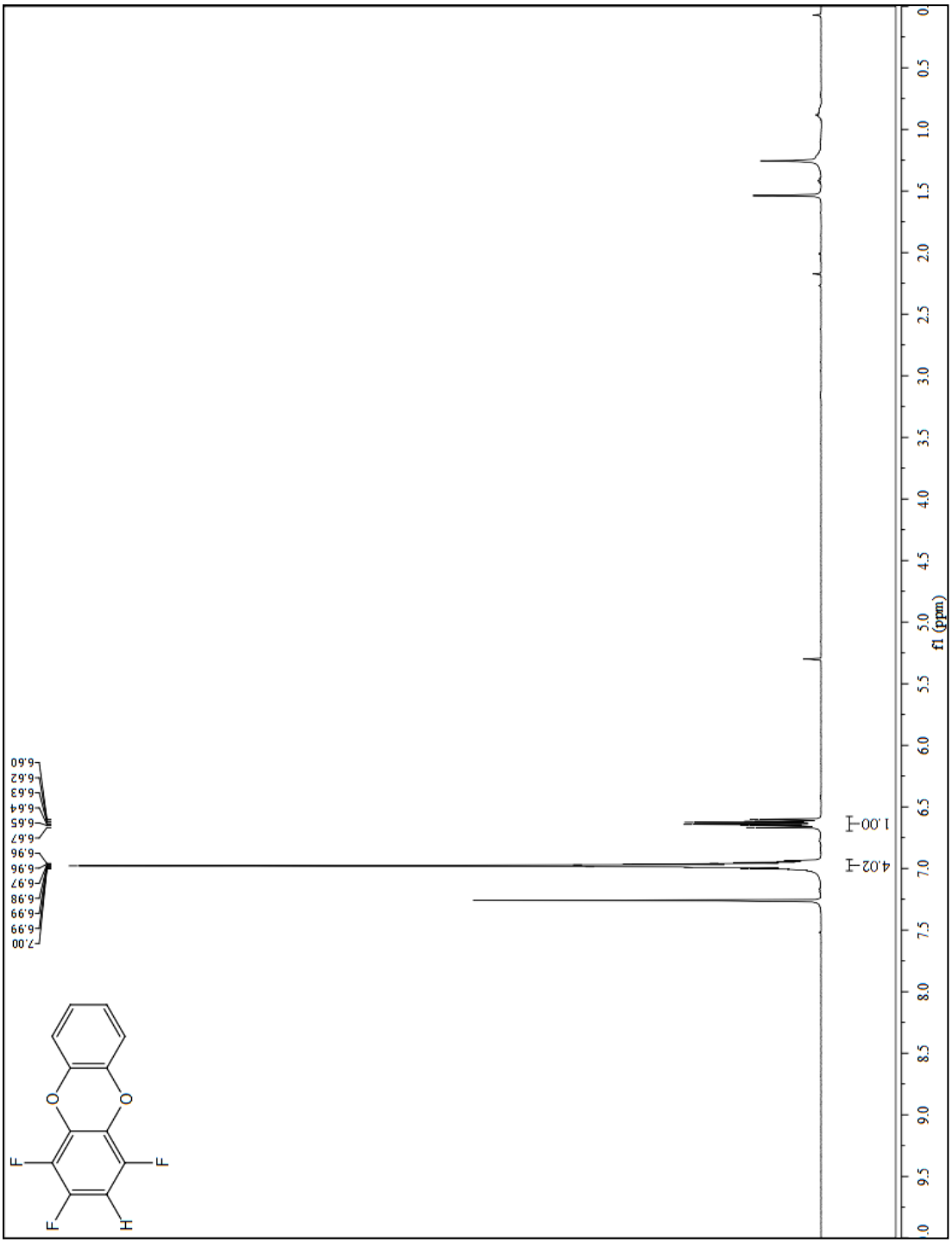
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7q (*N*-cyclohexyl-*N*-(2,3,5,6-tetrafluorophenyl)acetamide)



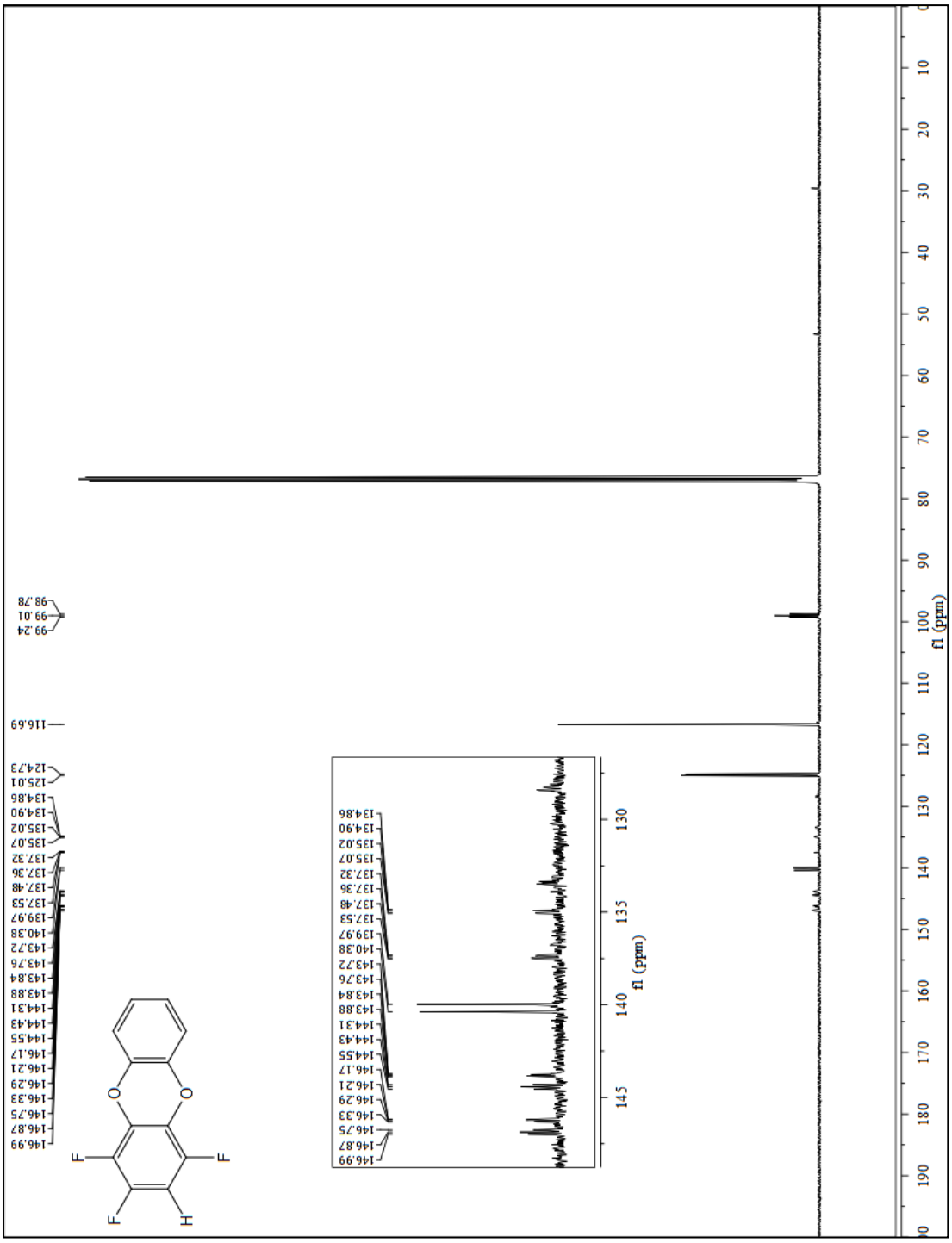
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7r (1,2,4-trifluorodibenzo[b,e][1,4]dioxine)



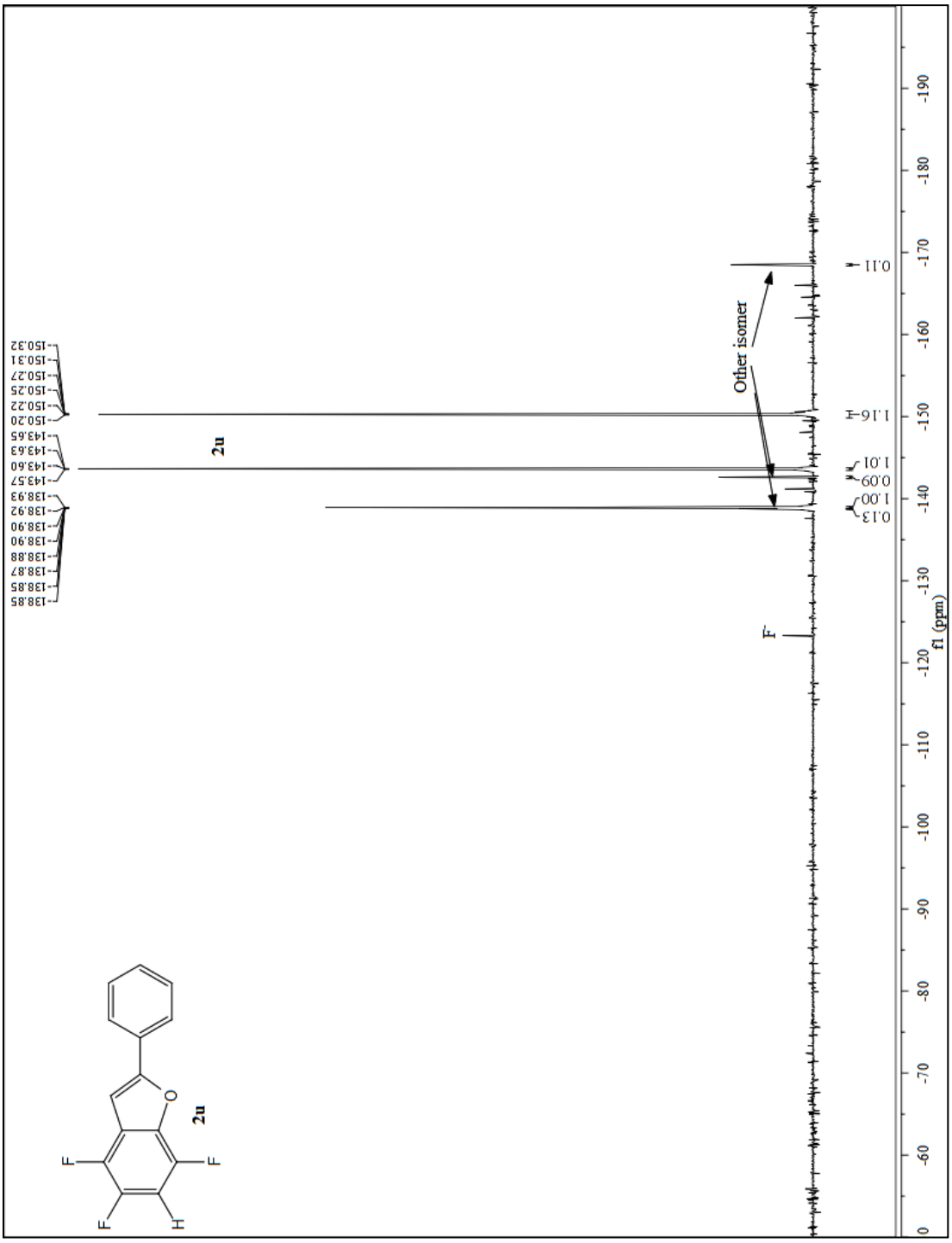
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7r (1,2,4-trifluorodibenzo[b,e][1,4]dioxine)



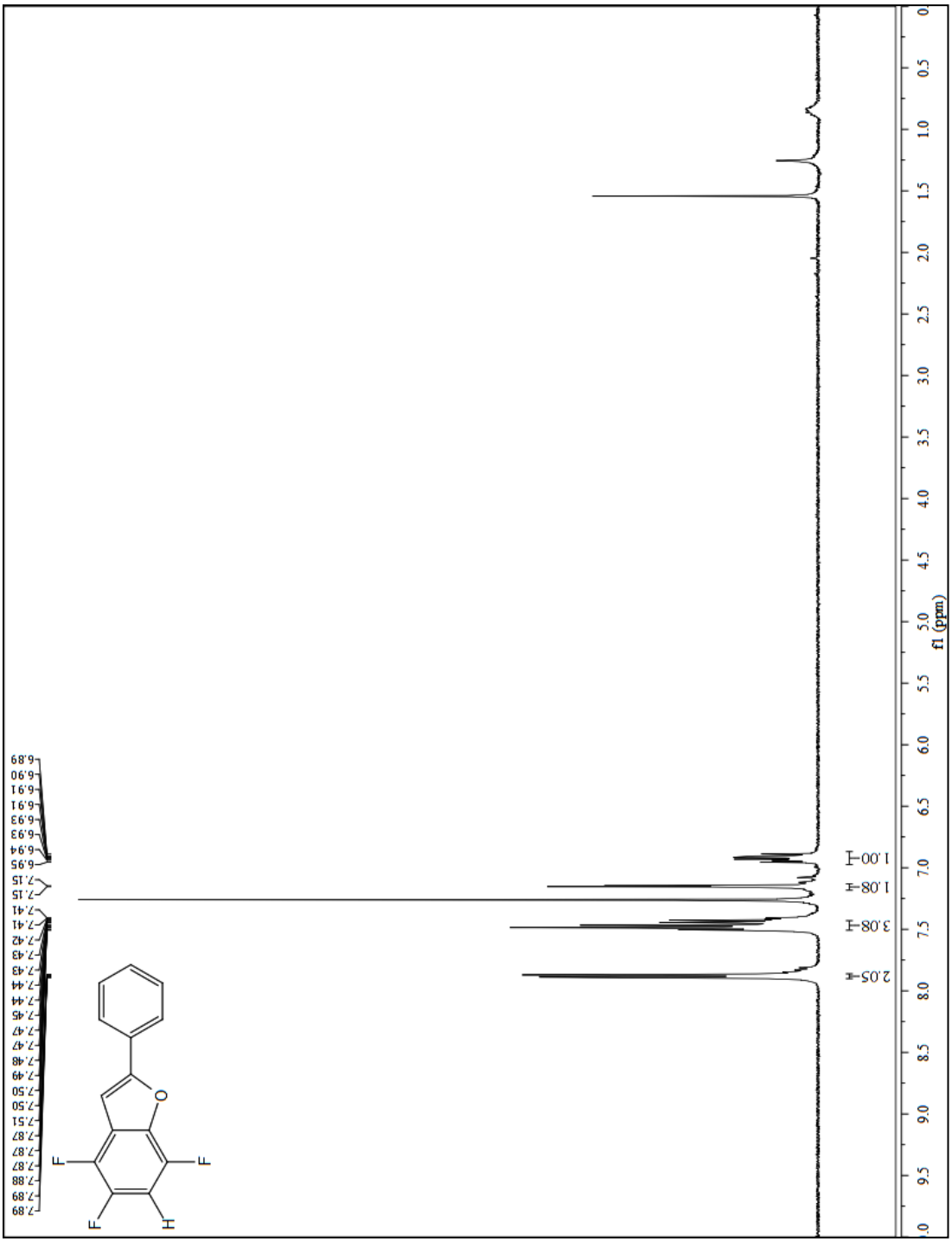
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7r (1,2,4-trifluorodibenzo[b,e][1,4]dioxine)



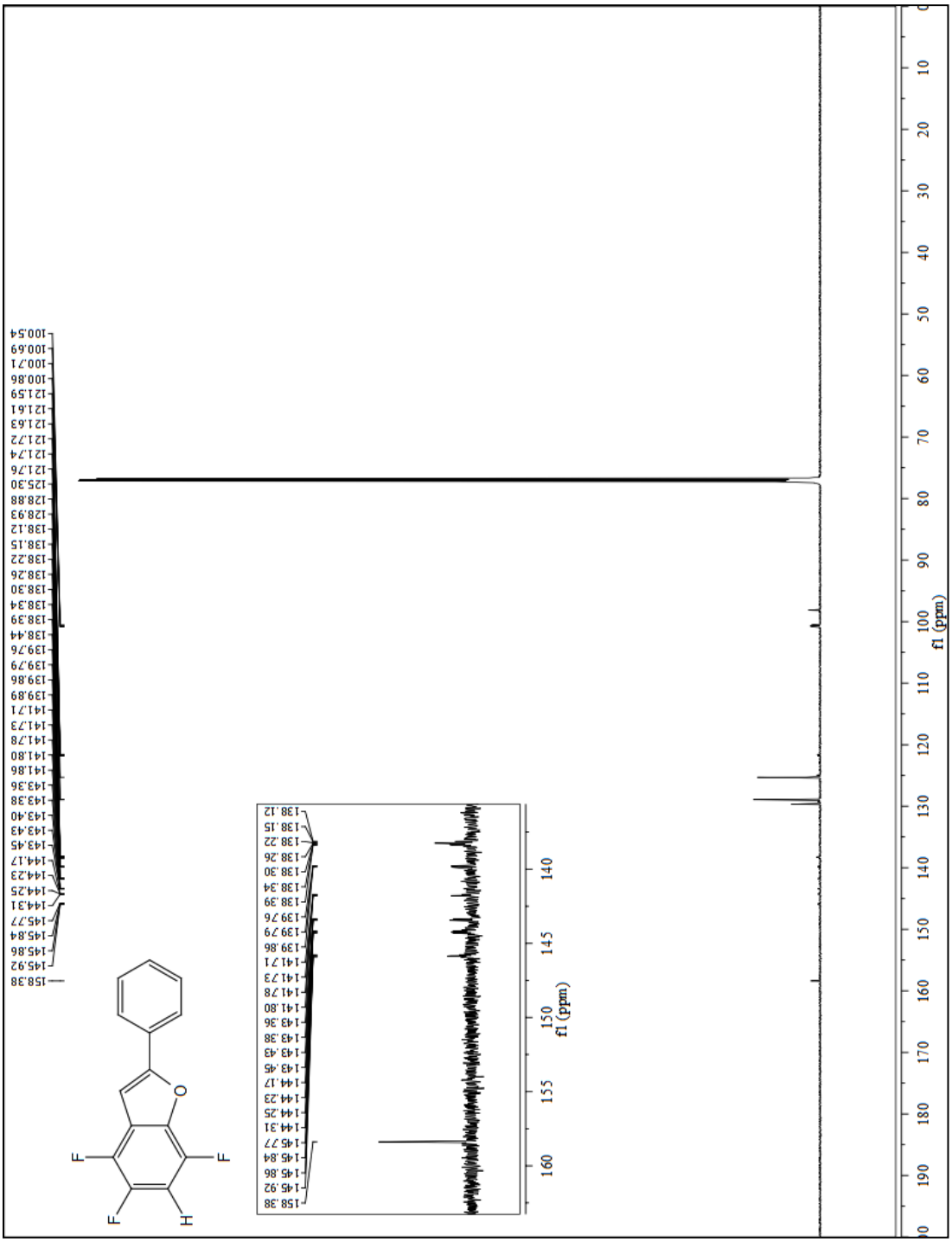
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7s (4,5,7-trifluoro-2-phenylbenzofuran)



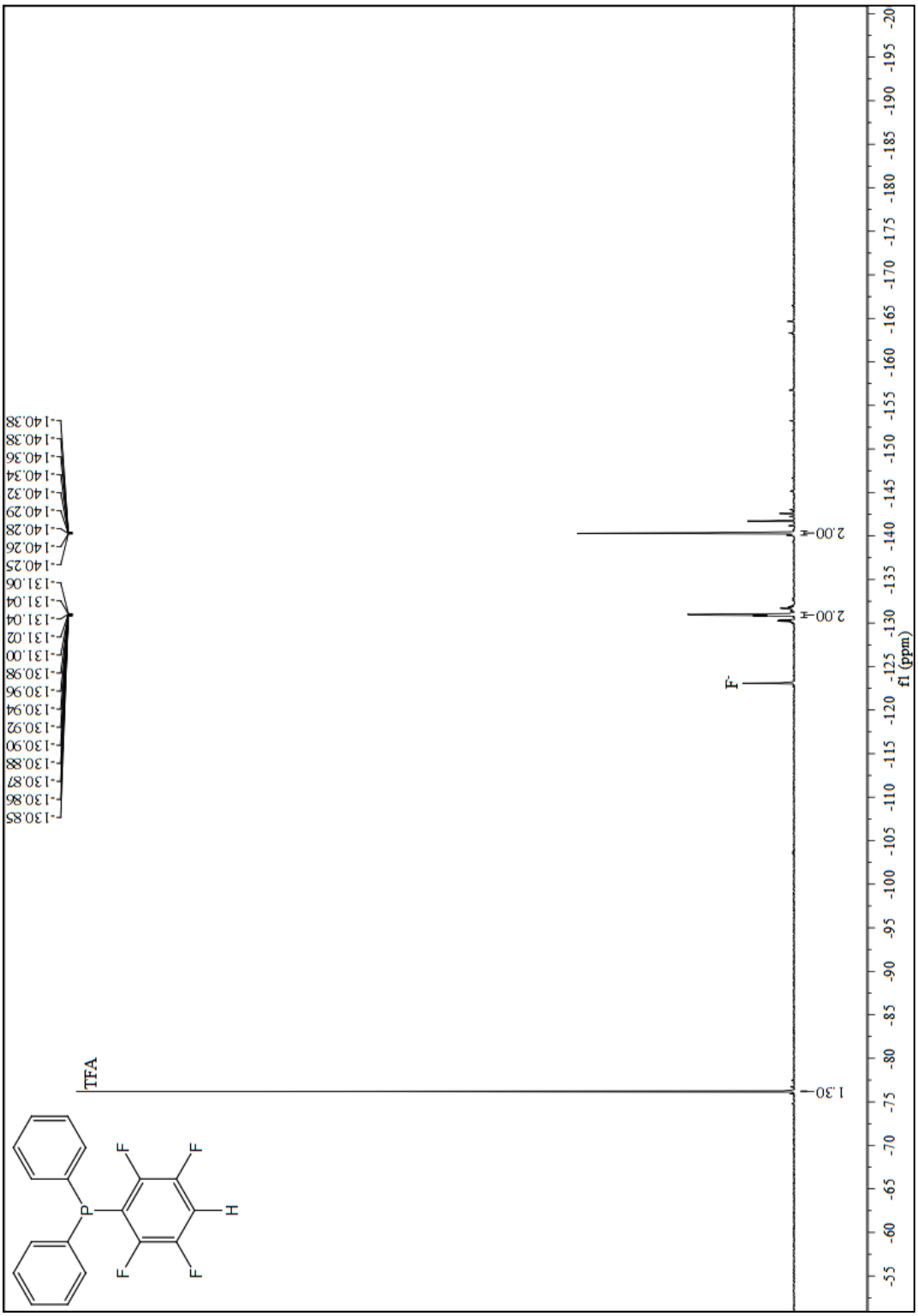
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7s (4,5,7-trifluoro-2-phenylbenzofuran)



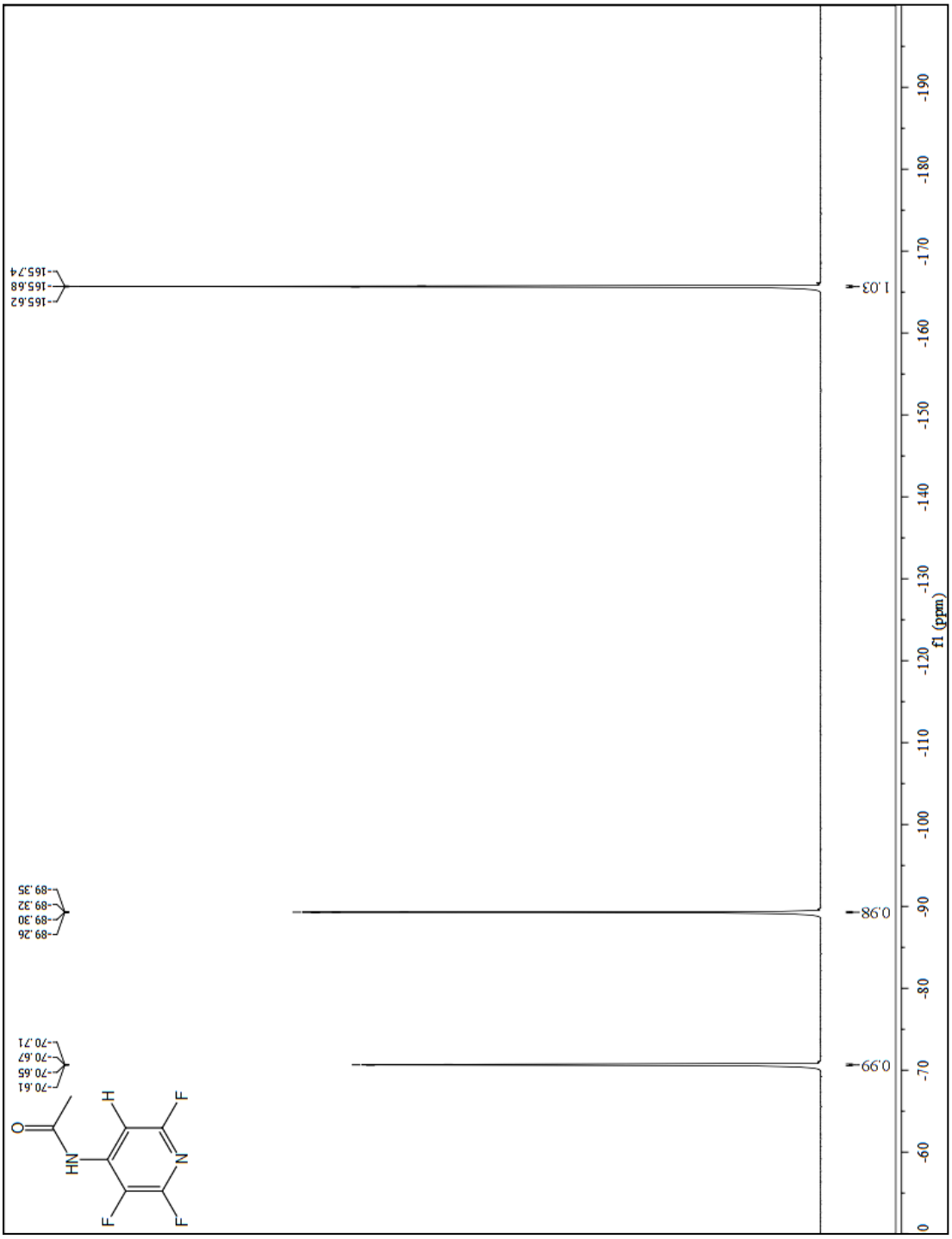
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7s (4,5,7-trifluoro-2-phenylbenzofuran)



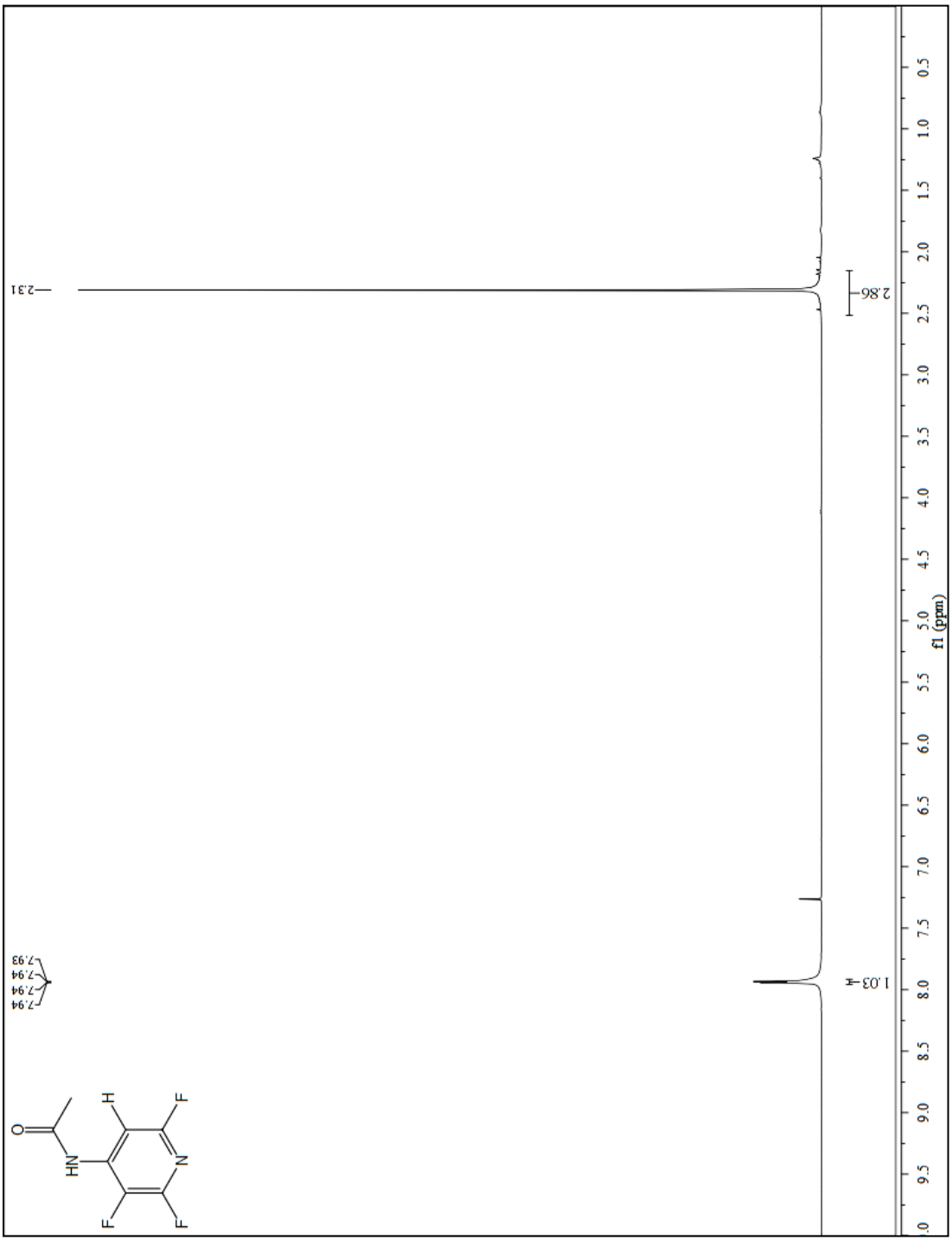
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7t (diphenyl(2,3,5,6-tetrafluorophenyl)phosphane)



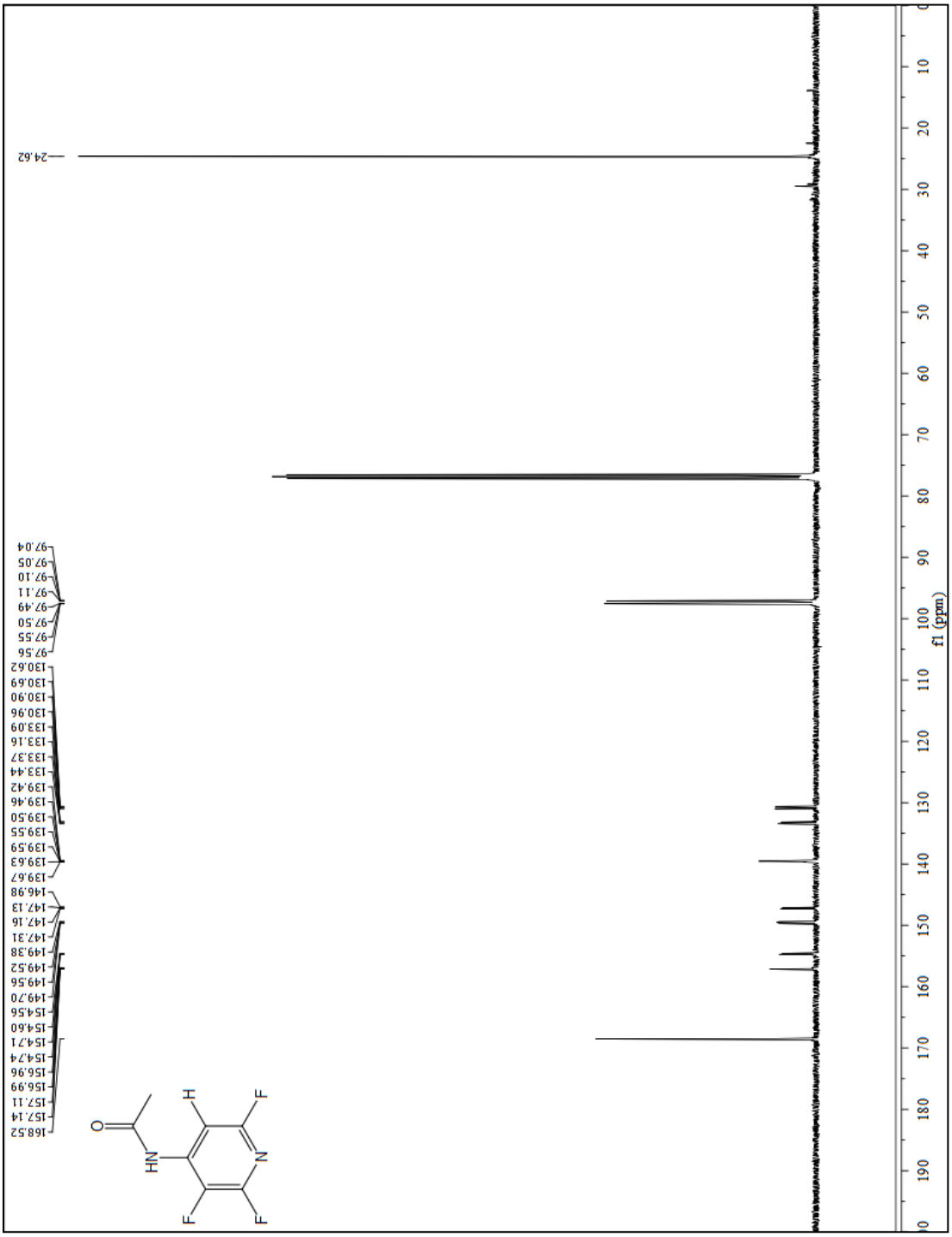
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7u (*N*-(2,3,6-trifluoropyridin-4-yl)acetamide)



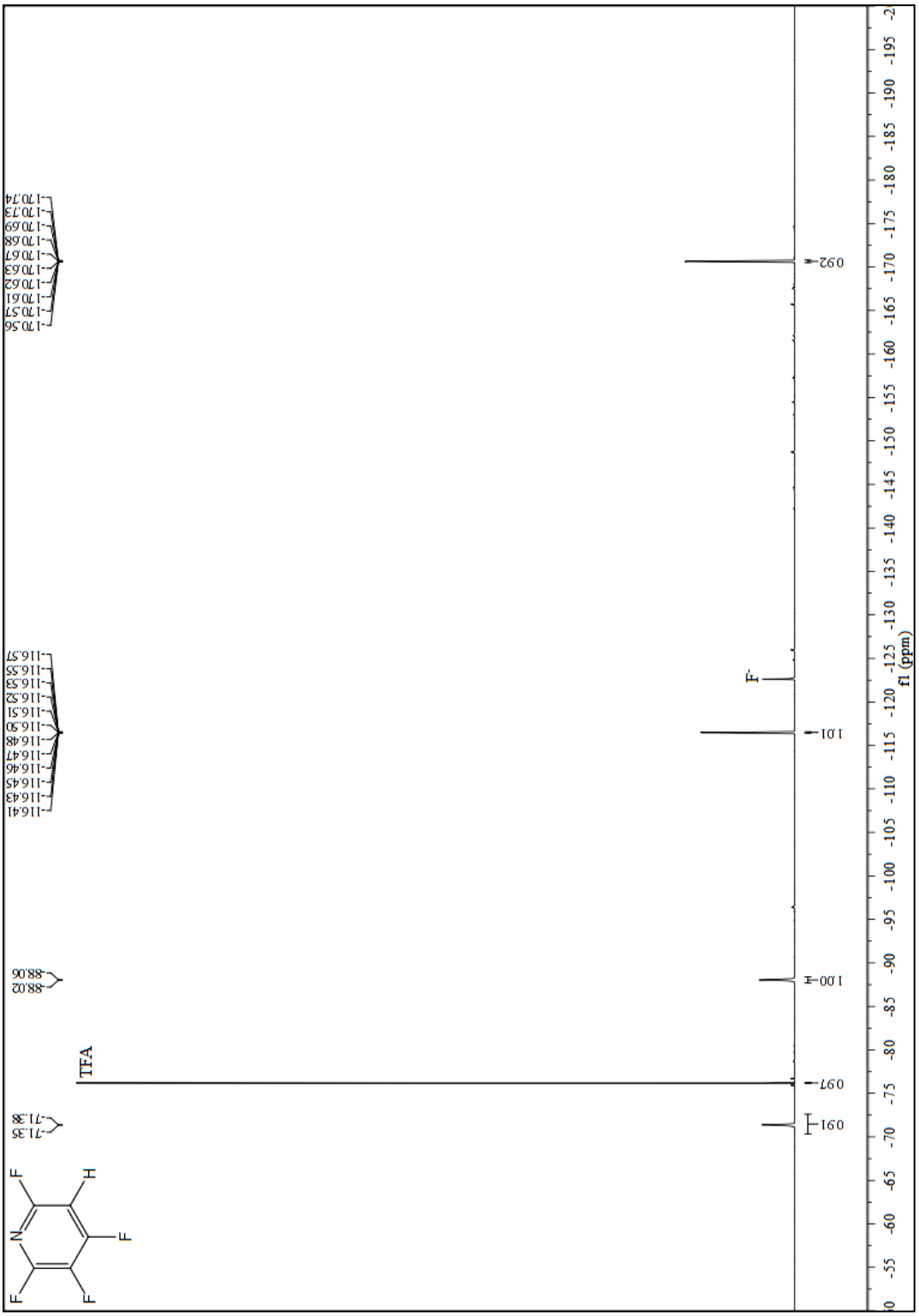
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7u (*N*-(2,3,6-trifluoropyridin-4-yl)acetamide)



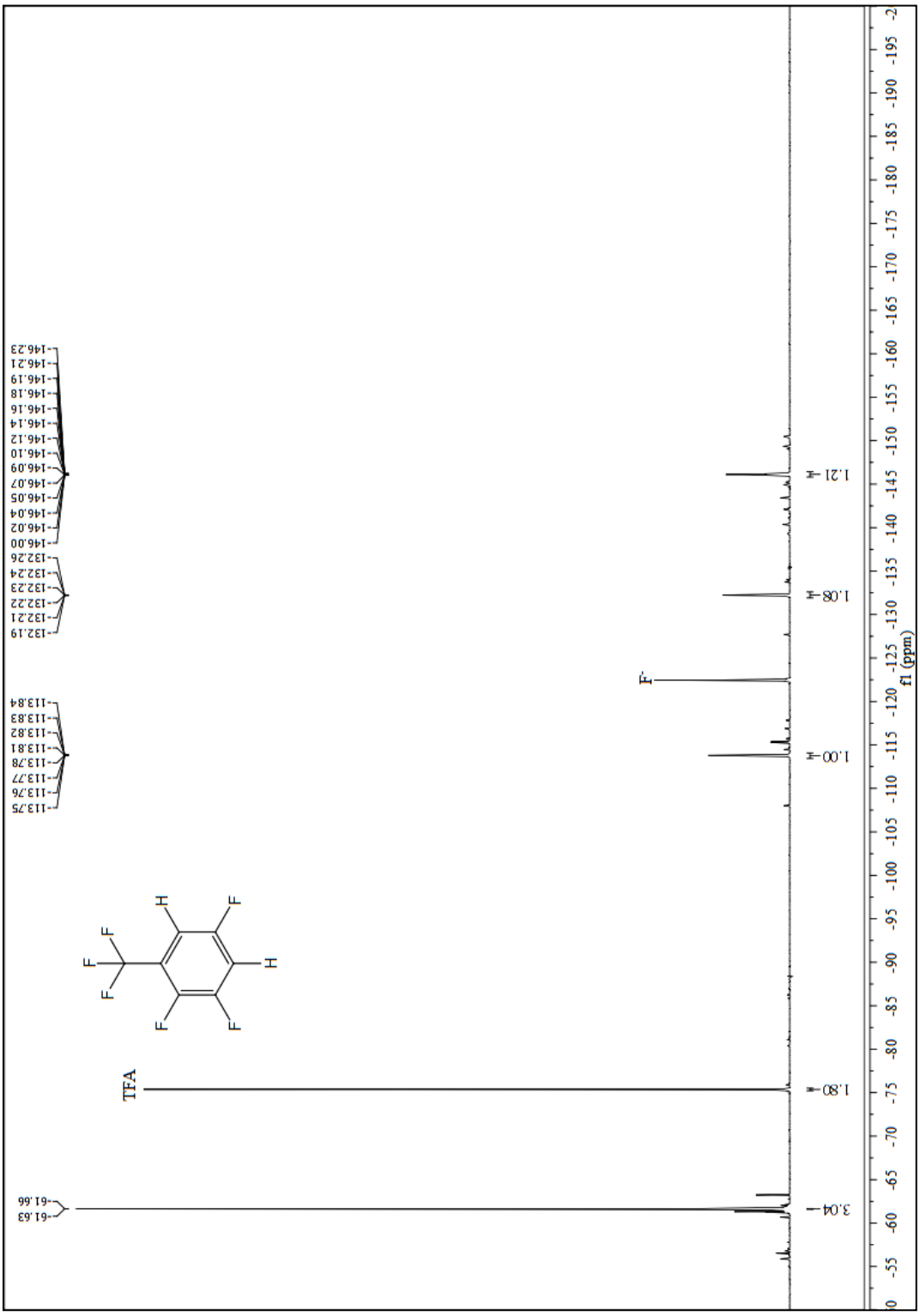
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7u (*N*-(2,3,6-trifluoropyridin-4-yl)acetamide)



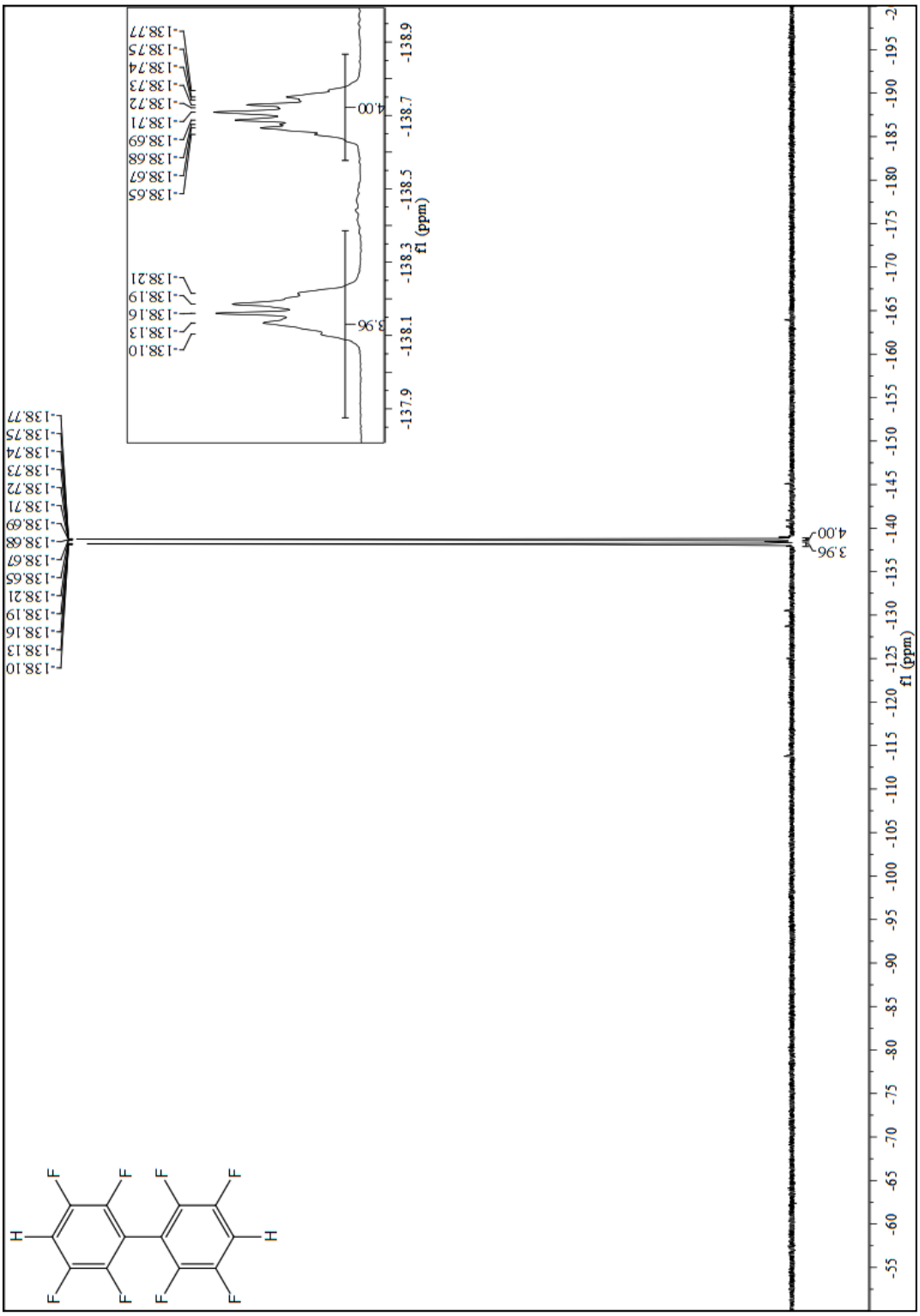
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.7v (2,3,4,6-tetrafluoropyridine)



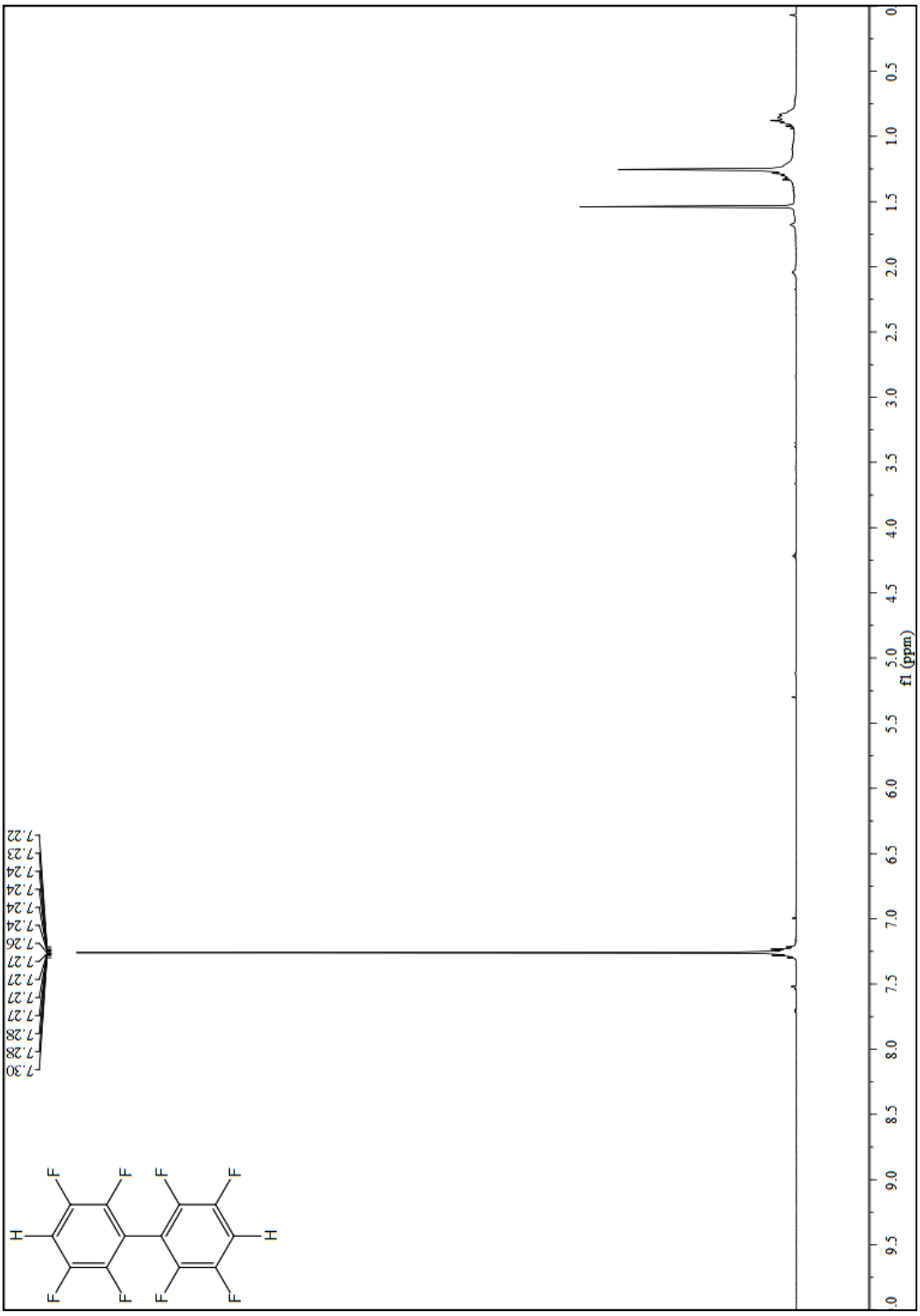
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8a (1,2,5-trifluoro-3-(trifluoromethyl)benzene)



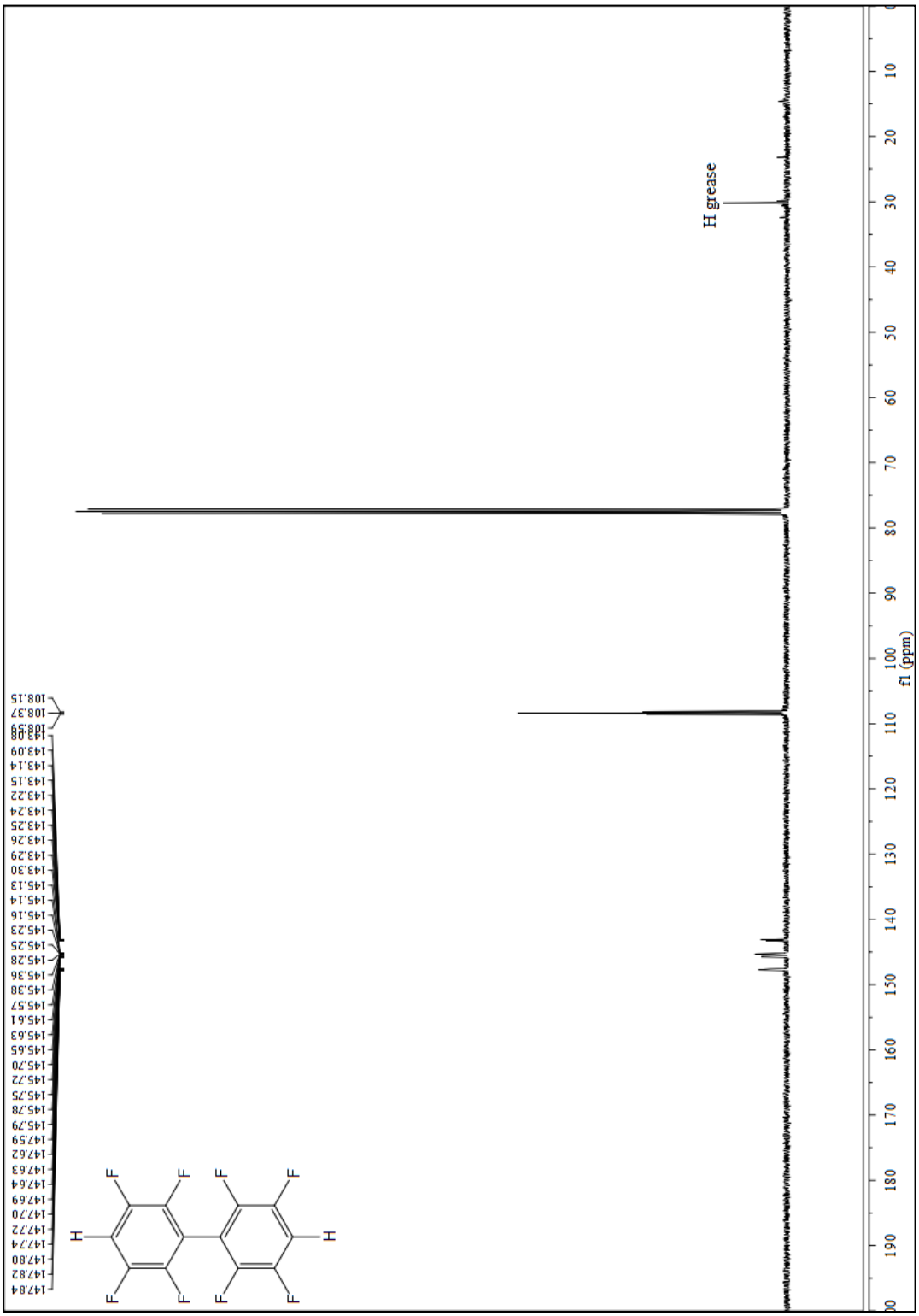
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8b (2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl)



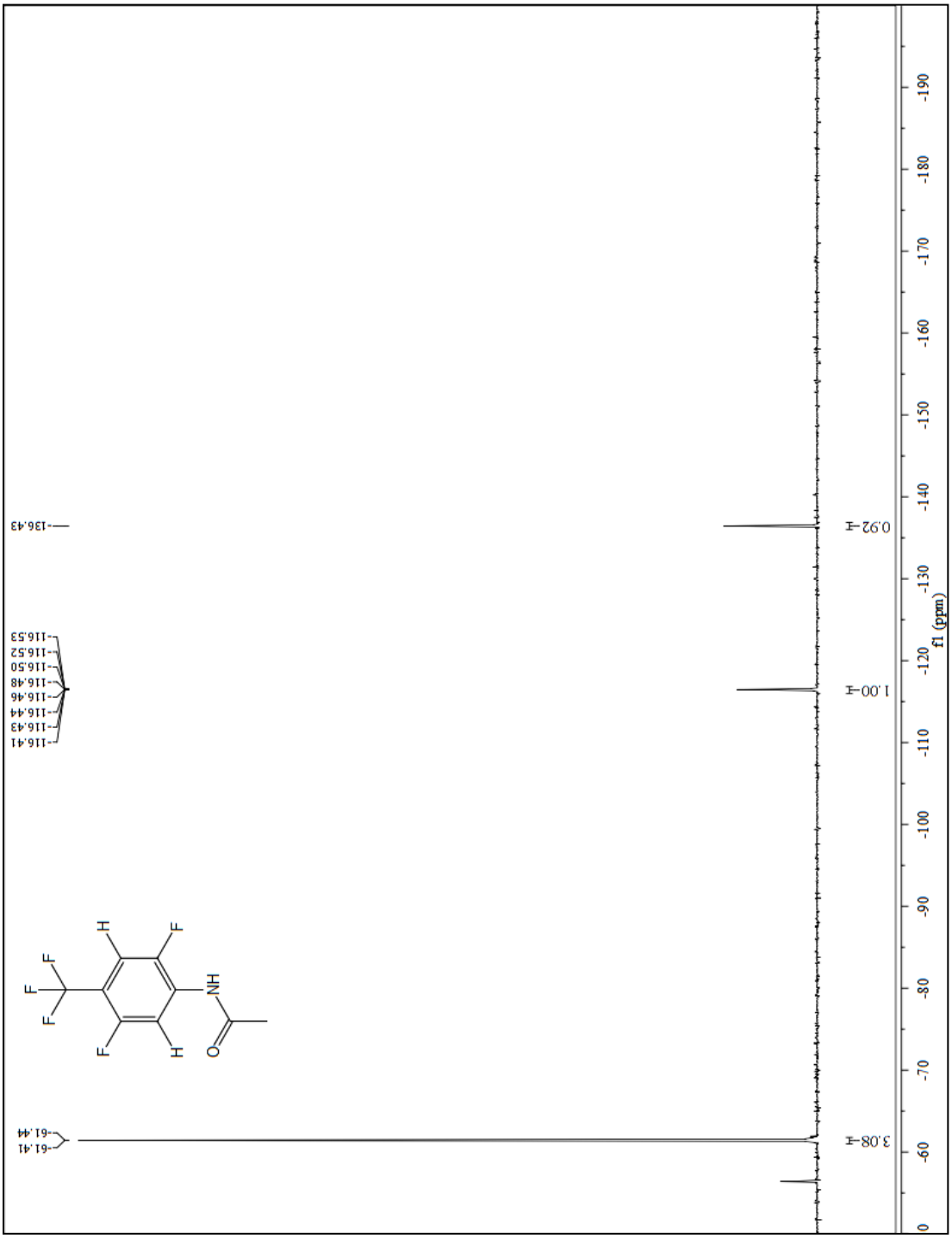
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8b (2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl)



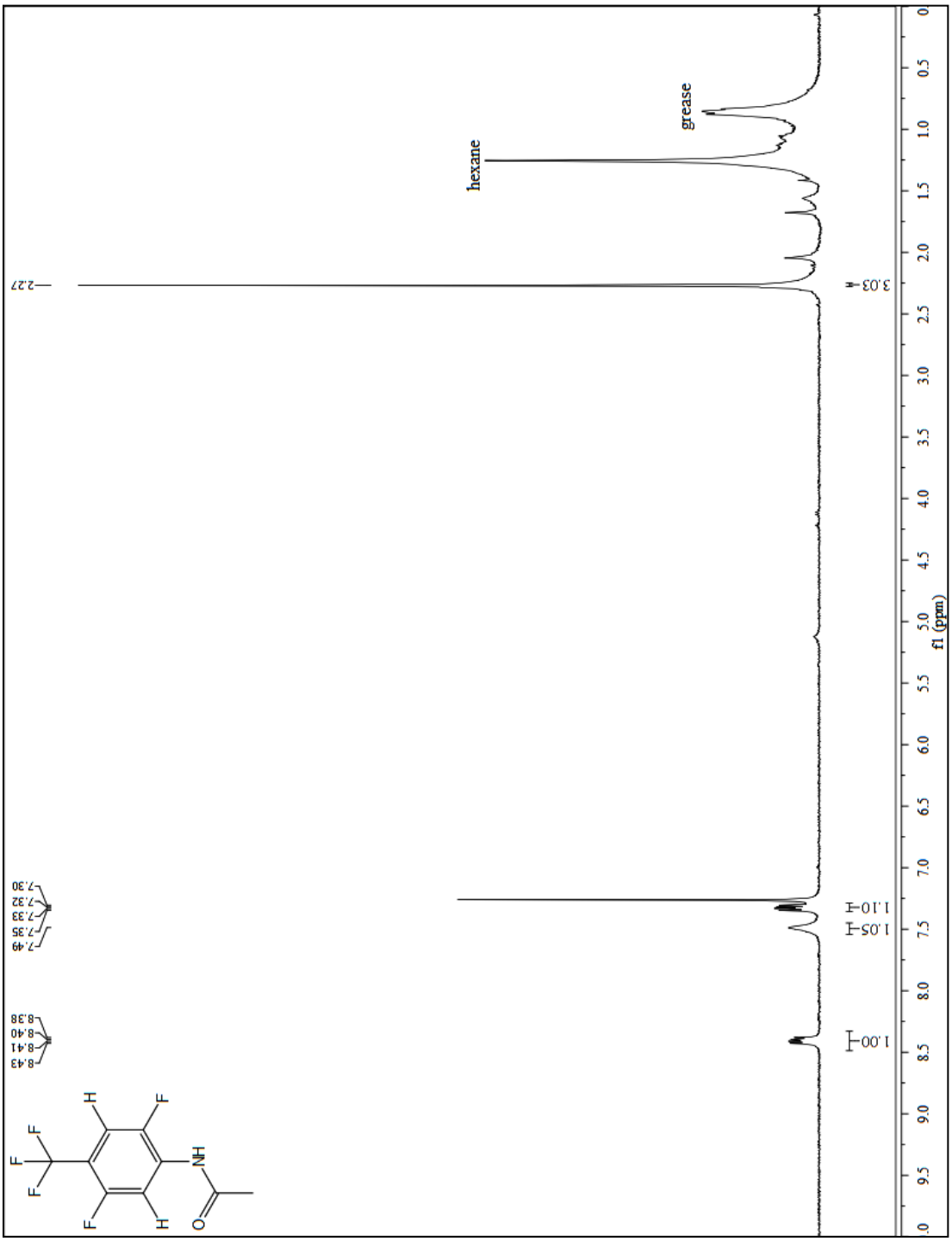
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8b (2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl)



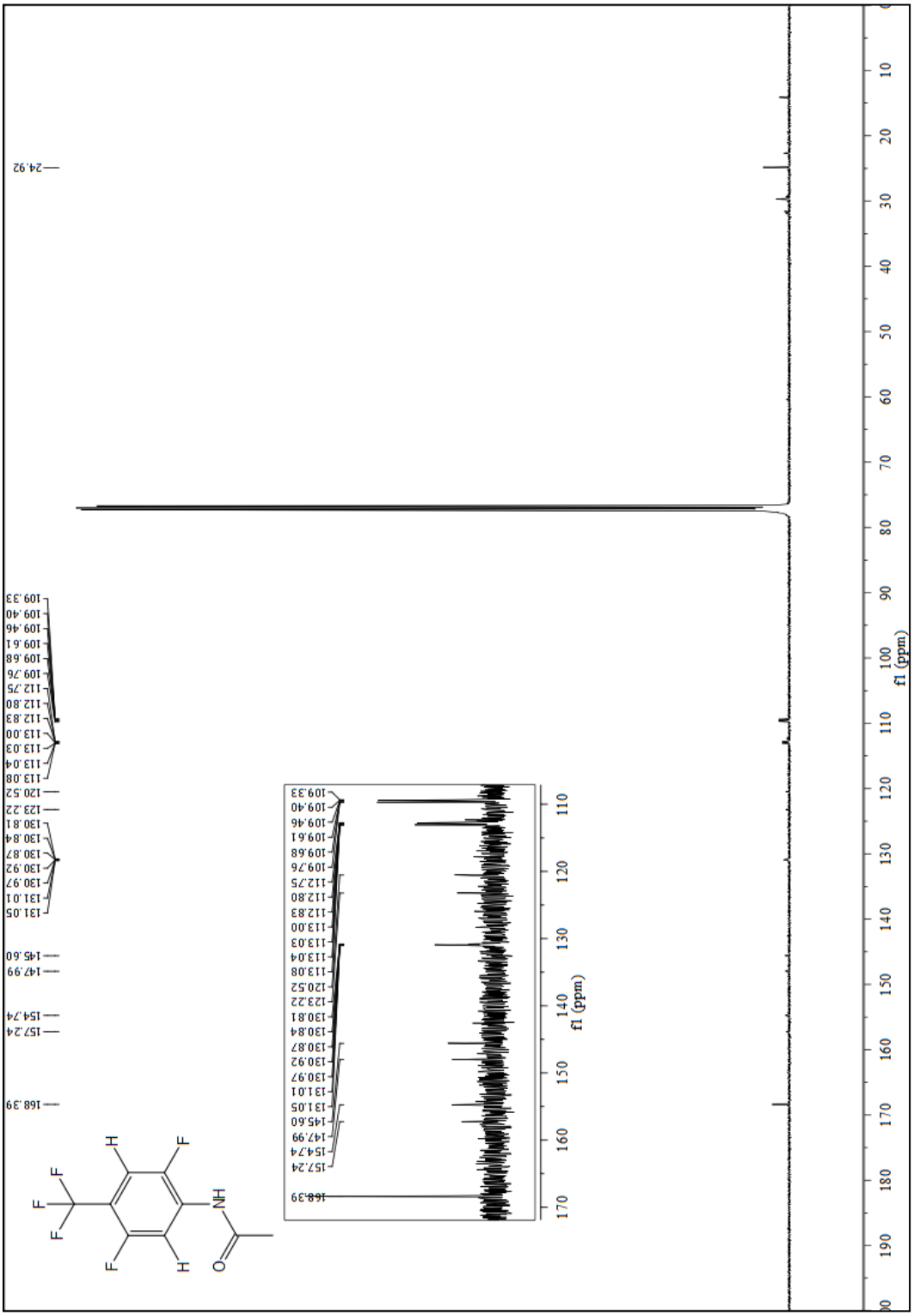
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8c (N-(2,5-difluoro-4-(trifluoromethyl)phenyl)acetamide)



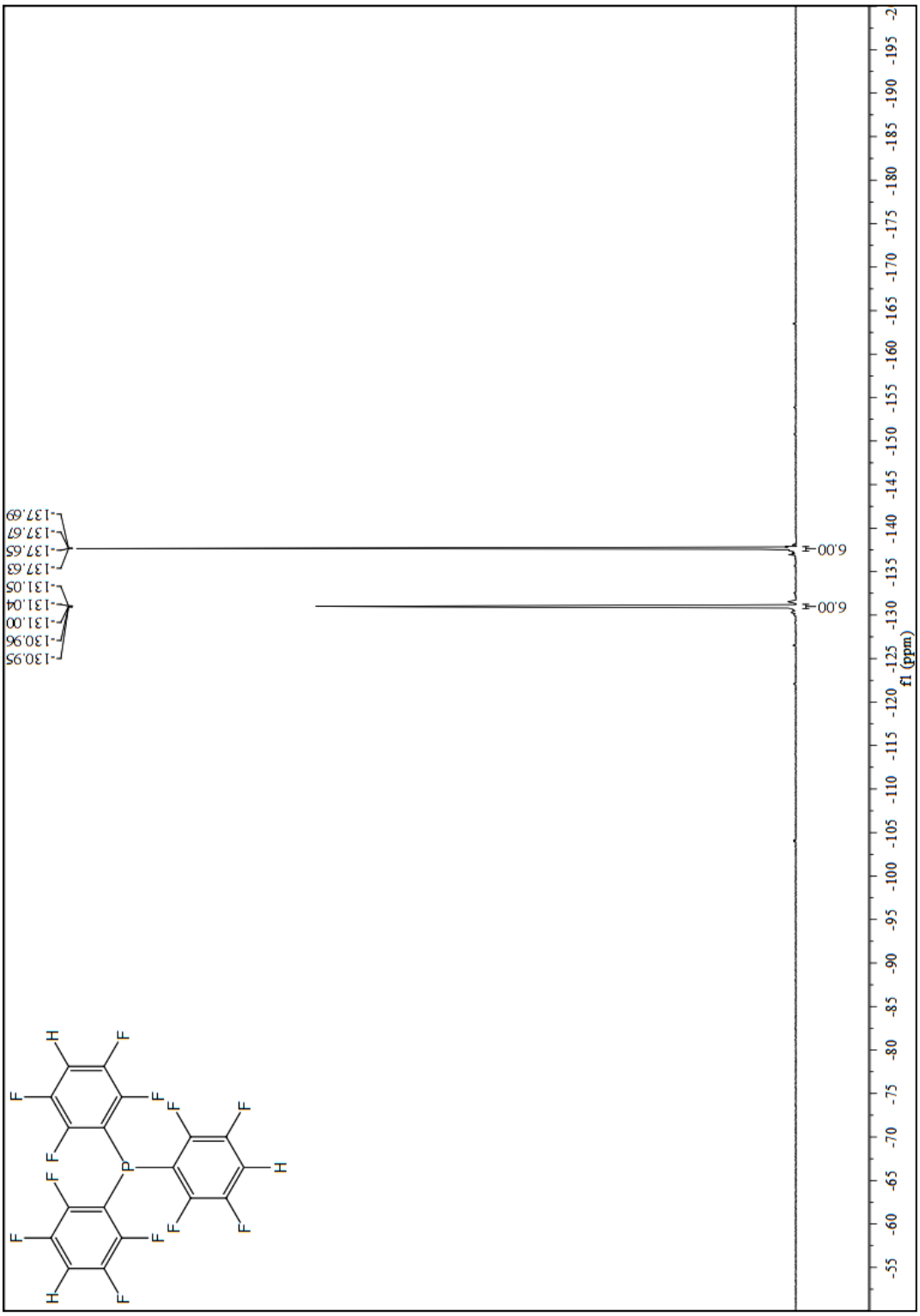
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8c (N-(2,5-difluoro-4-(trifluoromethyl)phenyl)acetamide)



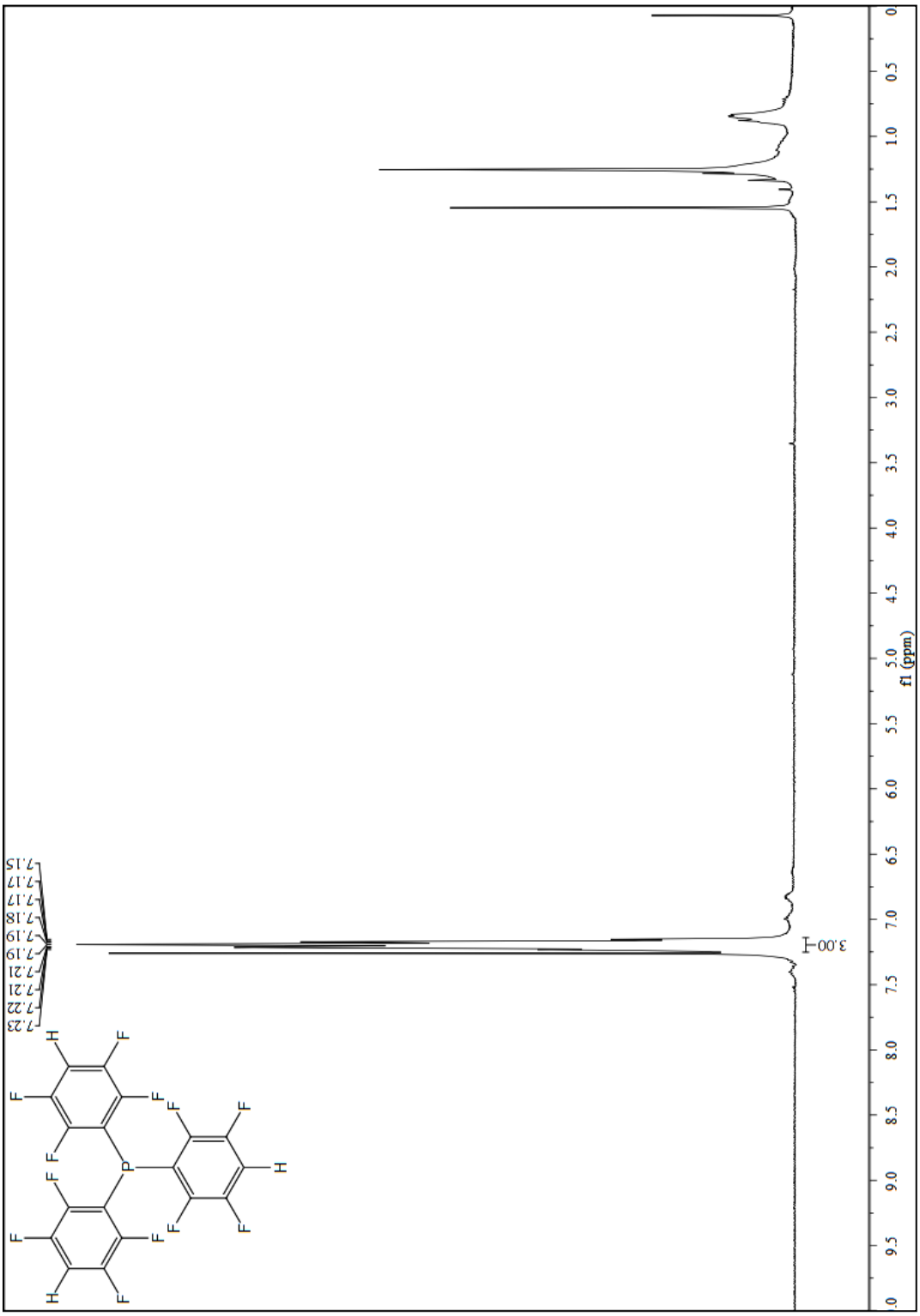
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8c (N-(2,5-difluoro-4-(trifluoromethyl)phenyl)acetamide)



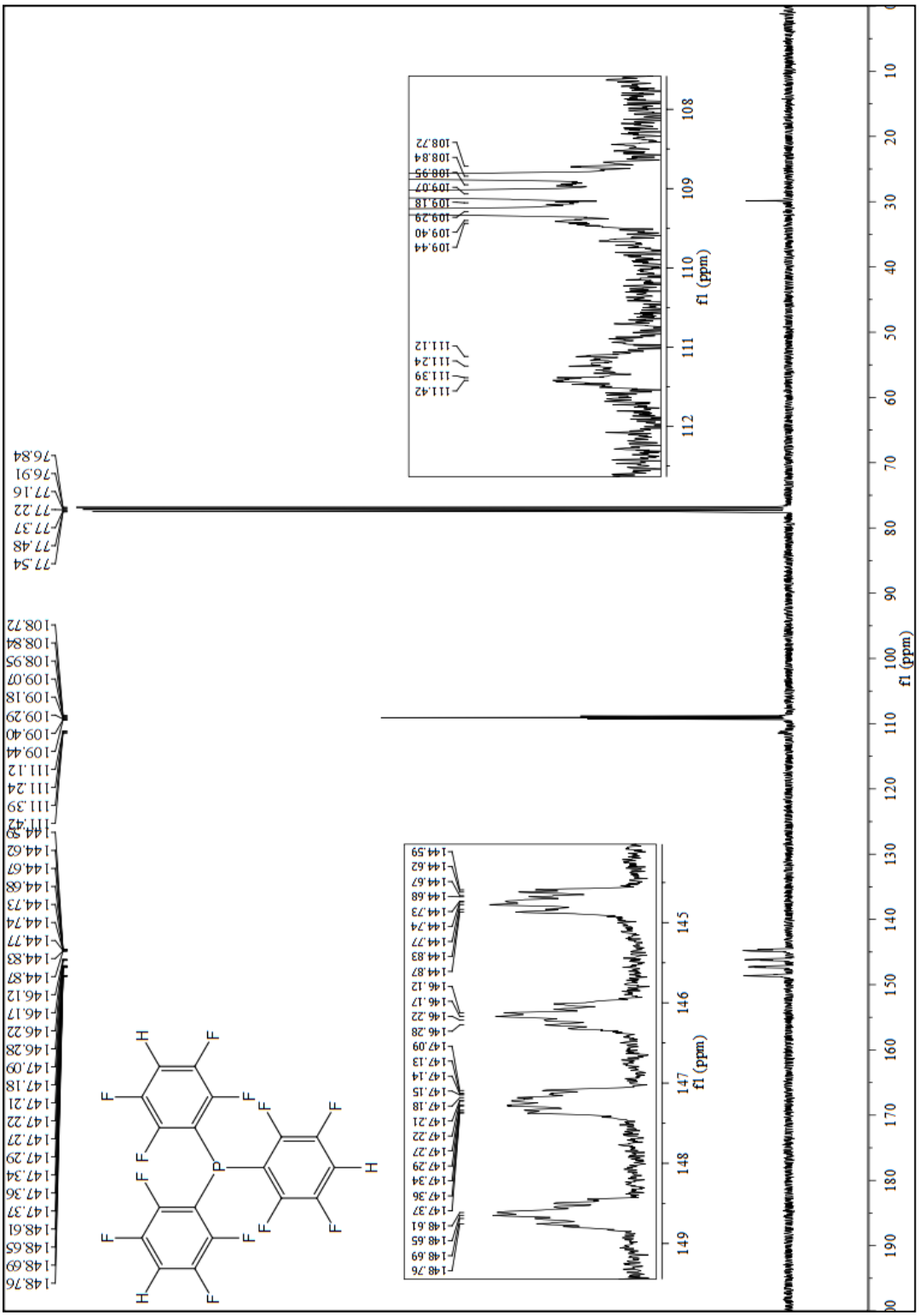
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8g (tris(2,3,5,6-tetrafluorophenyl)phosphine)



^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8g (tris(2,3,5,6-tetrafluorophenyl)phosphine)



^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2.8g (tris(2,3,5,6-tetrafluorophenyl)phosphine)



CHAPTER III

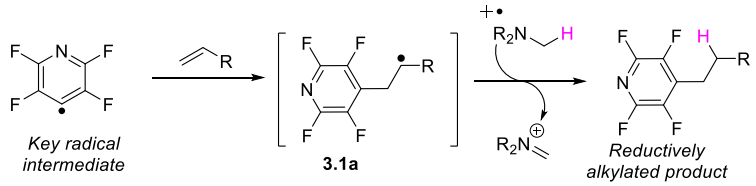
PHOTOCATALYTIC DUAL C–F, C–H FUNCTIONALIZATION TO ACCESS MULTIFLUORINATED BIARYLS

3.1 Introduction for photocatalytic C–C bond formation reactions

Development of the photo-HDF reaction showed that catalytic amounts of *fac*-Ir(ppy)$_3$ can result in the generation of a perfluoroaryl radical intermediate in the presence of light and an amine reductant. The radical can be reduced by abstracting an H-atom. Given that the ability of the reaction to perform highly efficient HDF with excellent regioselectivity and functional group tolerance,[16a] we envisioned that the *in-situ* generation of the perfluoroaryl radical might provide a novel route for direct C−F functionalization if the radical intermediate could be intercepted with a coupling partner other than an H-atom. With this in mind, our lab began to investigate the feasibility of using the photo-generated perfluoroaryl radical as a coupling partner. In 2015, the Weaver group demonstrated the ability to intercept the perfluoroaryl radical intermediate generated *in situ*, with alkenes to form the corresponding alkyl radical which then abstracted an H-atom to form the alkylated polyfluoroarene product.[55] The use of catalytically generated

radicals for C−C bond formation is attractive, because the addition takes place with relatively small energy barriers for the addition to π-bonds and also the energy barriers correlate strongly with the thermodynamics of addition. Given the expected exothermicity, the implication was that facile bond formation would allow to reaction of unactivated and sterically congested π-bonds. A variety of perfluoroarenes engaged in this photo-alkylation with unactivated alkenes to give alkylated products (Scheme 3.1).[55]

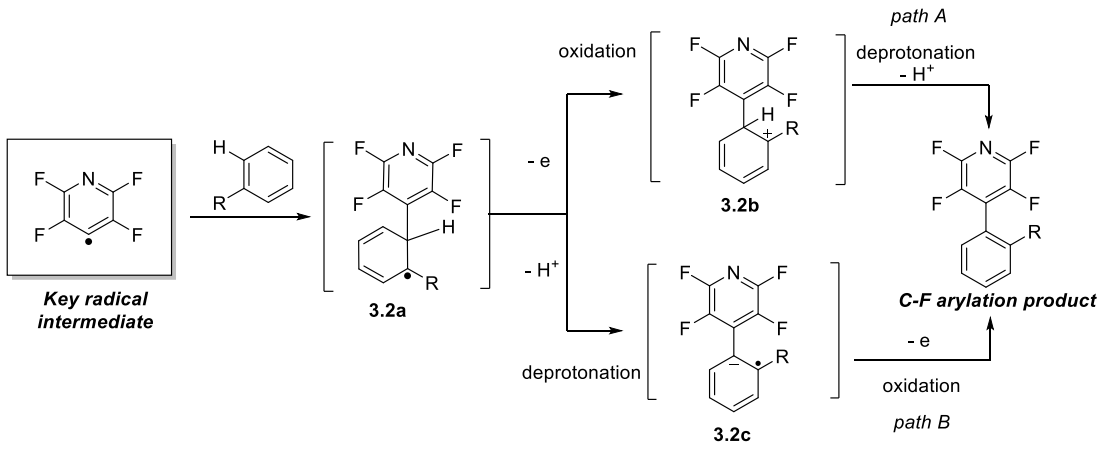
For the development of the photocatalytic C−F alkylation, it was necessary that the perfluoroaryl radical be intercepted with an alkene faster than H-atom transfer. The simplest strategy found to gain this product selectivity was to increase the alkene concentration in the reaction (i.e., 6 equiv of alkene), given that the alkenes are ubiquitous. Decreasing the amine reductant, in order to decrease the possibility of H-atom abstraction which leads to the HDF product, was not an option because of the need for an H-atom as the terminal reductant to reduce the fluoroalkyl radical (Scheme 3.1, **3.1a)**.



Scheme 3.1 Interception of the photo-generated perfluoroaryl radical with alkenes

At this point we wanted to know if we could intercept the perfluoroaryl radical with an arene-H, rather than an alkene, to generate multifluorinated biaryls. The addition of the perfluoroaryl radical to an alkene generates an sp^3 - hybridized alkyl radical (Scheme 3.1) and was expected to be exothermic.[56] Perfluoroaryl radicals are reactive intermediates that are capable of addition to the π-bonds of even trisubstituted alkenes.[55] In this regard, arenes can also be viewed as π-nucleophiles, which can undergo addition to the perfluoroaryl radical.[57] However, it was expected that the radical addition to H-arenes would be more complicated since addition

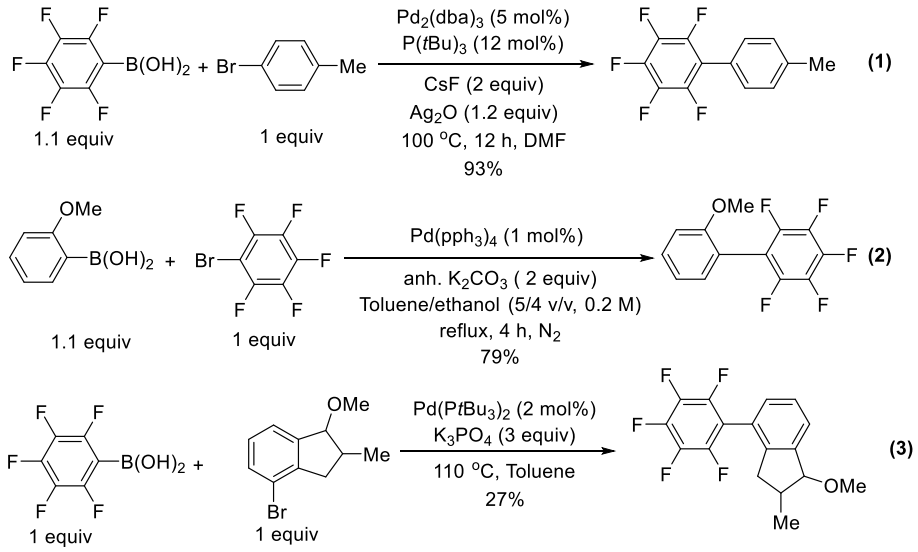
would result in dearomatization of the arene (Scheme 3.2). Upon bond addition to the perfluoroaryl radical, a cyclohexadienyl radical[58] (**3.2a**) would form. The simplest way to gain a full octet would be to either abstract an H-atom or to undergo a net oxidation event to regain aromaticity. If the latter is operative, it can happen either *via* a single electron oxidation followed by a deprotonation (path A) or *vice versa* (path B), and in reality the path is likely substrate dependent. With electron rich arene-Hs, path A becomes more likely, whereas with electron poor arene-Hs deprotonation followed by an oxidation (path B) becomes more probable.



Scheme 3.2 Plausible mechanistic pathways of photo-arylation

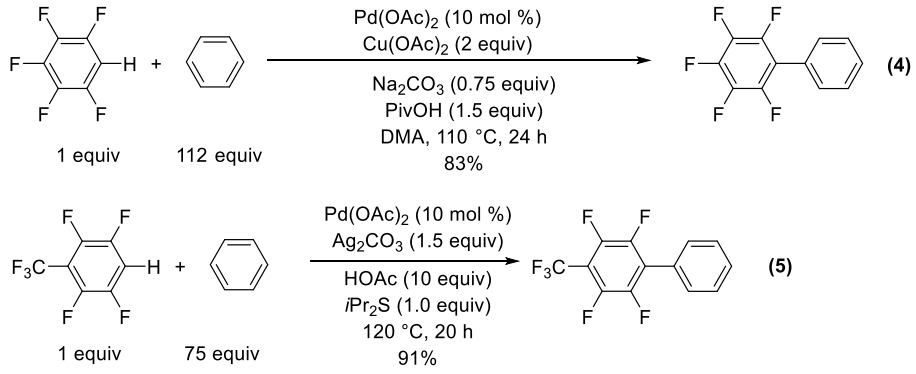
Emergence of cross-coupling methods made biaryls generally accessible.[59] However, there are far fewer methods exist that lead to the important class of partially fluorinated biaryls. The synthesis of such molecules has been approached from several different directions. Importantly, all the methods require prefunctionalization of at least one coupling partner. The most common and probably most viable method is to use a fluorine-containing arene possessing either an organometallic (eq 1) or a halogen (eq 2) group with a coupling partner substituted with a complementary reactive group. In other words, both partners are derivatized prior to reaction.[47d, 60] Use of boronic acids[61], boronic esters, and trifluoroborates are used in these applications.[62] Such methods employ boron bearing reagents on the arene-H, due to the

instability of polyfluoroboron reagents under the basic reaction conditions.[60a] Moreover, common perfluoroboronic acids are inactive substrates under the usual reaction conditions, because the transmetalation of the highly electron-deficient perfluoroaryl group to the Pd-center proceeds only with difficulty.[60b] Therefore, most of these reactions suffer from low yields (eq 3).[63] However, some attempts to use perfluoroboron reagents were also fruitful (Scheme 3.3).[60a, 60b]



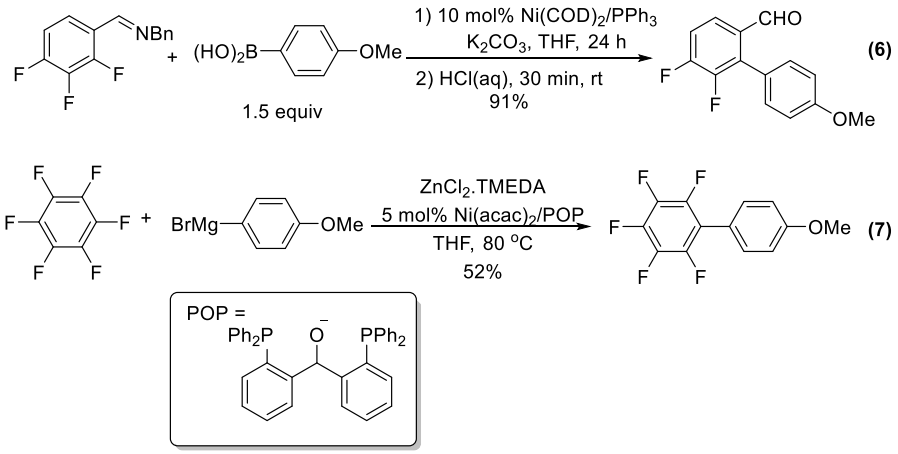
Scheme 3.3 Some successful biaryl formations using per(poly)fluoroboron reagents

Rarely, dual C–H activation has also been used as a strategy to couple the hydro-fluoroarenes with H-arenes to access multifluorinated biaryls (Scheme 3.4).[47e, 57, 64] It is worth noting that the existing methods of this kind require a large excess of arene–H, and typically used as the solvent for the reaction. While this is acceptable for simple H-arenes, this would be problematic when a late stage functionalization of a valuable H-arene is performed.



Scheme 3.4 Dual C–H activation to synthesize multifluorinated biaryls

While advances have been made in the formation of fluorinated biaryls, most typically activated multifluoroarenes are utilized in the coupling, and involve a multistep sequence of reactions starting from commercially available perfluoroarenes. First, the perfluoroarenes are reduced to install an aryl C–H[16b] bond, which can then be converted to a C–halogen[65] bond, and finally to a C–organometallic[66] reagent which is sufficiently activated to use as a cross-coupling reagent. To shorten the circuitous process of accessing this structurally simple, but hard to access motif, efforts have focused on direct C_{aryl}–F functionalization,[67] and have realized some success. As depicted in Scheme 3.5, these methods include directing group assisted *ortho* C–F arylation (eq 6)[67a] and a nickel-catalyzed cross-coupling between a polyfluoroarene and organozinc reagents (eq 7).[67c] However, these methods also require the functionalization of the H-arene, and in doing so fails to take full advantage of the pre-functionalized nature of the arene-F.



Scheme 3.5 Selected examples for direct C–F functionalization to form per(polyfluoro) biaryls

Developing a method which could perform dual C–F, C–H functionalization would avoid the difficulties associated with the prefunctionalization of coupling partners and shorten the overall synthetic sequence. Furthermore, it would allow the use of commercially available perfluoroarenes and arene-Hs directly, as opposed to more highly derivatized molecules. At the outset, we sought to investigate the ability to intercept the photocatalytically generated perfluoroarylradical with arene-Hs. It was expected that realizing this goal would rapidly provide access to a broad range of new fluorinated compounds that were previously inaccessible.

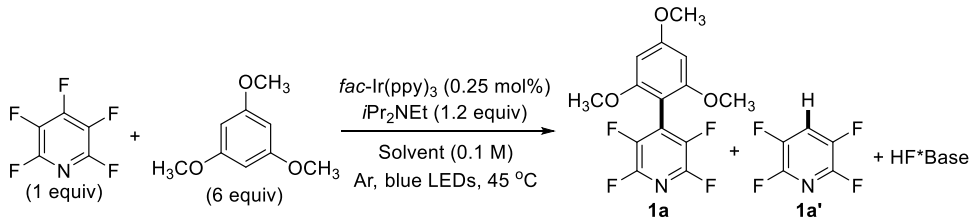
3.2 Development of photocatalytic arylation of per- and polyfluoroarenes

To commence our investigations, we identified the challenges associated with the desired reaction. The photocatalytically generated perfluoroaryl radical is generated under strongly reducing conditions, because both the reduced $Ir(ppy)_3^-$ (-2.19 V *vs.* SCE) and photoexcited $Ir(ppy)_3$* (-1.73 V *vs.* SCE) are strongly reducing. However, synthesis of the product required an oxidation of the intermediate to achieve rearomatization under these reducing reaction conditions was less than a certain outcome. Furthermore, it was anticipated that the competing HDF would also be problematic. Nonetheless, we began our investigation with conditions that had facilitated HDF[16a] using pentafluoropyridine as the perfluoroarene. We were enlightened and encouraged by

the results of the photocatalytic alkylation[55] reaction, in which the use of 6 equiv of alkene demonstrated that formation of the undesired HDF could be largely avoided. Thus, we decided to use 6 equiv of 1,3,5-trimethoxybenzene as a starting point. Trimethoxybenzene was selected as the arene-H for optimizations to remove the possibility of having regioisomers that might otherwise complicate monitoring the process by ^{19}F NMR. We were pleased to see that the desired C−C coupled product was formed as the major product in reasonable yield, along with a significant amount of the HDF-product (Table 3.1, entry 1).

Reaction optimization was carried out, in hopes of increasing the yield, and simultaneously decreasing the amount of the arene-H coupling partner. First, a survey of solvents was performed as depicted in Table 3.1. Both DMF and DMSO provided the desired product, albeit in lower yields than MeCN, while DCM and THF resulted in low yields of undesired products. Therefore, we simply concluded to avoid halogenated, and nonpolar solvents which have lower dipole moment (~1.6). MeCN was chosen for further optimizations.

Table 3.1 Solvent optimization of photo-arylation reaction



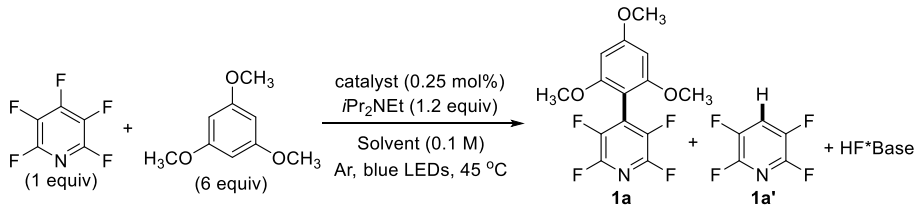
entry	solvent	dipole moment of the solvent	**1a**:**1a'**	conversion to **1a**[a]	time, h
1	MeCN	3.9	5:1	47/73%	3/19[b]
2	DMF	3.8	1:2	22/31%	3/19[b]
3	DMSO	3.9	3:1	58/58%	3/19[b]
4	DCM	1.6	no reaction		3/19
5	THF	1.6	no reaction		3/19

[a] Determined by ^{19}F NMR, [b] Reaction complete

After obtaining satisfactory conversion using MeCN we turned our attention to the catalyst's structure to modulate the reactivity. Using a pool of iridium photocatalyts[68] a catalyst

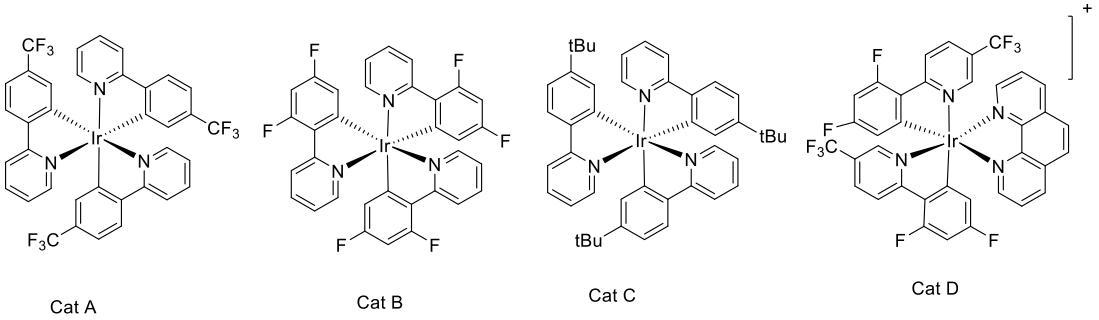
screen was carried out, which assessed the ability to influence the product ratio and yield. Unfortunately, while we found several catalysts that were able to make the product ratio significantly worse, only one catalyst resulted in a better **1a**/**1a'** ratio. Despite the slightly improved product ratio, an overall worse yield of **1a** was achieved due to decreased conversion.

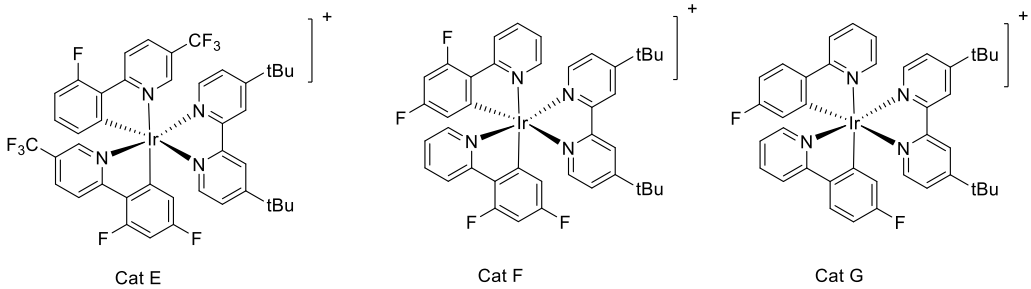
Table 3.2 Catalyst screen



entry	catalyst	**1a**:**1a'**	conversion to pdt (**1a**)[a]	time, h
1	*fac*-Ir(ppy)$_3$	5:1	47/73%	3/19[b]
2	Cat A	6:1	10/52%	4/19[b]
3	Cat B	no reaction		4/19
4	Cat C	0.2:1	5/12%	4/19
5	Cat D	no reaction		4/19
6	Cat E	2.6:1	15/24%	4/19
7	Cat F	2.5:1	8/27%	4/19
8	Cat G	6:1	14/31%	4/19

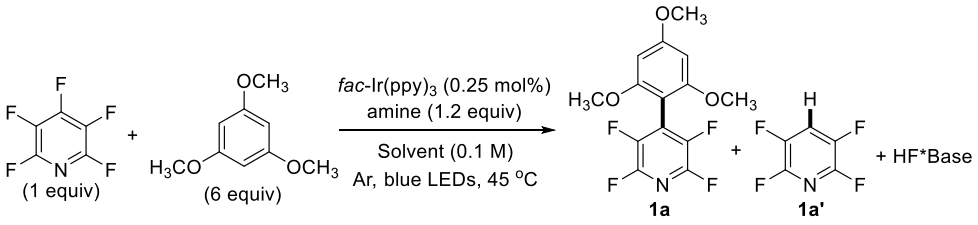
[a] Determined by ^{19}F NMR, [b] Reaction complete





As discussed in chapter 2, the amine serves dual roles in the HDF reaction. It acts as the electron source and as an H-atom donor for the reduction. In contrast to the HDF reaction, the desired arylation does not require an H-atom donor, and only transiently needs an electron to initiate the process. Therefore, the amine's role is likely limited to serving as an electron donor. The electron should be recovered in the reoxidation of the dearomatized intermediate. Consequently, sub-stoichiometric amine should be enough to promote the reaction. Therefore, we evaluated both the structure of the amine and its loading as reaction parameters. While Et_3N worked reasonably well, it led to products stemming from *N*-perfluoroarylation byproducts. The formation of byproducts was substantially decreased by use of more sterically cumbersome diisopropylethyl amine (*i*Pr_2NEt) and dicyclohexylethyl amine (Cy_2NEt) which gave comparable results. Regardless, *i*Pr_2NEt was chosen for further optimizations due to its low cost (*i*Pr_2NEt, $ 80/mol *vs.* Cy_2NEt, $ 960/mol). With the varying amounts of amine an obvious trend was observed. When the amine was superstoichiometric, the consumption of the starting material was faster, but led to greater amounts of HDF product.

Table 3.3 Investigation of the effect of the amine

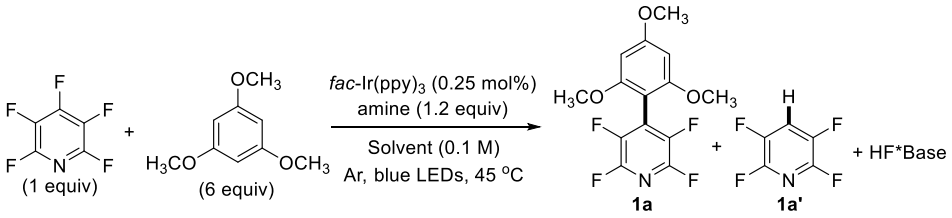


entry	solvent	**1a**:**1a'**	conversion to **1a**[a]	time, h
1	*i*Pr_2NEt	5:1	58/75%	5/19[b]
2	Et_3N	4:1	47/66%	5/19[b]
3	*i*Pr_2NH	no reaction		5/19
4	Cy_2NEt	5:1	40/75%	5/19[b]
5	no amine	na	<5%	2/17[c]
6	0.5 equiv *i*Pr_2NEt	6:1	22/ 79%	2/17[b]
7	3.0 equiv *i*Pr_2NEt	3:1	40/61%	2/17[b]

[a] Determined by ^{19}F NMR [b] Reaction complete. [c] <20% conv. to undesired products.

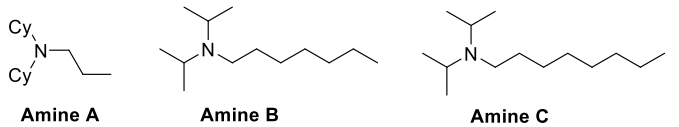
Given that the more amine has a negative effect on product ratio we started considering alternative ways to keep the effective amine concentration low but, enough to promote the reaction. In 2015, the Weaver group, showed that the use of less soluble amine could retard the rate of the photocatalytic reduction[69] in the photoinduced reductive alkylation of 2-bromoazoles. It was hypothesized that the use of such poorly soluble amines effectively maintained a low amine concentration, and resulted in less reduction product. This may stem from the fact that the aryl radicals can also abstract an H-atom directly from the amine, rather than the amine radical cation. To test this idea, we carried out photocatalytic arylation with different low soluble amines in MeCN (Table 3.4). Unfortunately, except Cy_2NPr (amine A), all the other amines tested dramatically slowed the reaction.

Table 3.4 Efforts to optimize with less soluble amines in the photo-arylation reaction



entry	amine	solubility in MeCN at 23 °C	**1a**:**1a'**	conversion to **1a**[a]	time, h
1	*i*Pr_2NEt	1.3 M	5:1	22/ 79%	2/17[b]
2	Amine A	0.036 M	5:1	15/ 65%	2/17[b]
3	Amine B	0.15 M	na	<5%	2/17[c]
4	Amine C	0.099	na	<5%	2/17[c]
5	Amine D	0.077	na	<5%	2/17[c]
6	Amine E	-	na	<5%	2/17[c]

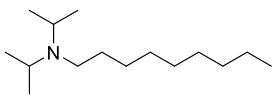
[a] Determined by 19F NMR, [b] Reaction complete, [c] reaction did not go beyond 15% conv



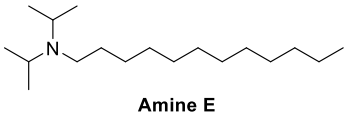
Amine A

Amine B

Amine C



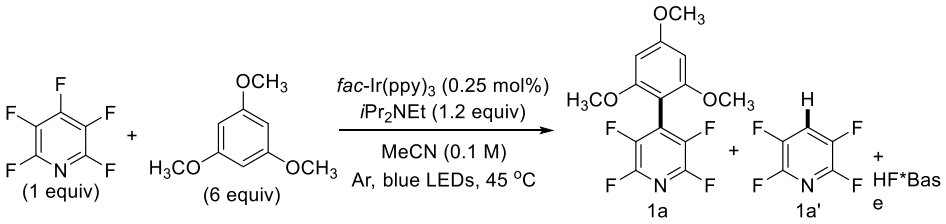
Amine D



Amine E

Next, we investigated the effect of reducing the amount of trimethoxybenzene, in hopes that we could approach near stoichiometric ratios between the two arene starting materials (Table 3.5, entry 2-3). Reducing the amount of arene-H resulted increased amounts of HDF product due to the competitive photo-HDF. Temperature can affect significantly on the product selectivity when multiple products can be generated from a common intermediate. Both the photo-arylation product and the photo-HDF product are generated from the same perfluoroaryl radical intermediate. Therefore, lowering the temperature would help selectively produce the product with a smaller activation barrier. Interestingly, lowering the reaction temperature led to a substantial improvement in the ratio of desired to HDF product (entry 4). Finally, we suspected that the amine was serving two roles, both as a reductant that initiates the C–F fragmentation as well as a base to scavenge the HF which is formed in the reaction. The latter role, however, required stoichiometric base. In hopes of further lowering the amine concentration, by avoiding its protonation, we added $KHCO_3$ as an external base (entry 5) which allowed us to simultaneously reduce the both the amine and trimethoxybenzene loading and achieve a satisfactory ratio of **1a**:**1a'**. Finally, control reactions were carried out, which indicated the necessity of light, catalyst, and amine. Furthermore, they indicated sensitivity towards air (entry 6-9).

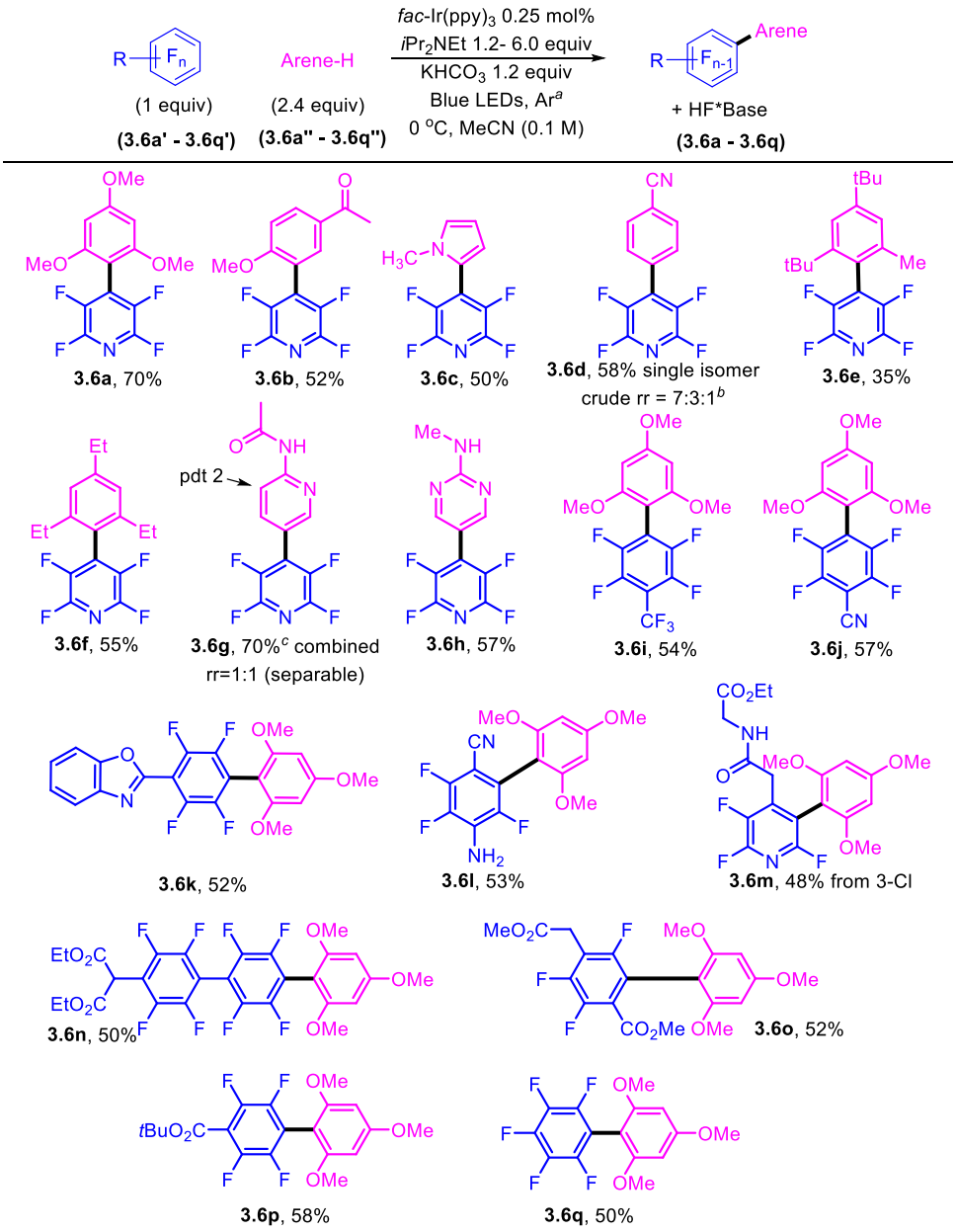
Table 3.5 Reaction optimization and control experiments



entry	modification	1a:1a'	conversion to 1a[a]	time, h
1	none	5:1	47/73%	3/19[b]
2	1.2 equiv. of arene-H	2:1	57%	17[b]
3	3.0 equiv. of arene-H	3.5:1	66%	17[b]
4	0 °C with 3.0 equiv arene-H	6:1	75%	19[b]
5	0 °C with 2.4 equiv arene-H, 0.4 equiv *i*Pr$_2$NEt and 1.2 equiv $KHCO_3$	13:1	71%	24[b]
6	same as 5 with no DIPEA	na	1%	24
7	same as 5 with no *fac*-Ir(ppy)$_3$	na	not detected	24
8	in air	na	11%	19
9	in dark	na	not detected	19

Having the optimized conditions in hand, we next evaluated the scope of the reaction (Table 3.6). We were pleased to see a variety of perfluoroarenes (**3.6a**, **i-q**) engaged in the arylation with good yields. More importantly, both electron-rich arenes-Hs (**3.6a"**, **c"**, and **e"-f"**) and electron deficient arenes such as acetophenones (**3.6b"**), and nitriles (**3.6d"**) engaged in the reaction with moderate to good yields. Arylation of sterically congested C_{aryl}–H bonds represents a formidable synthetic challenge by classical methods, but represents a useful class of compounds.[70] So, it is noteworthy that our method is able to utilize the perfluoroaryl radical to form even highly congested C−C bonds (**3.6e** and **3.6f**).

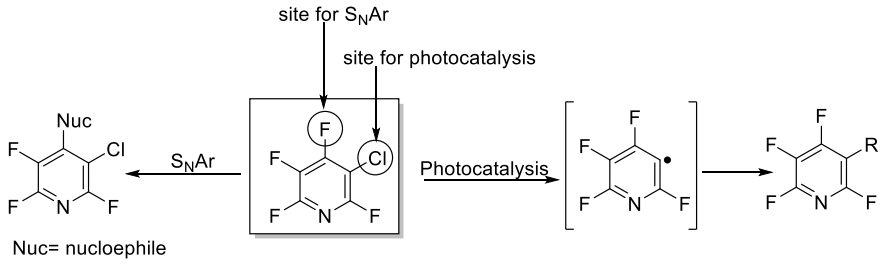
Table 3.6 Scope of photo-arylation reaction



[a] The reaction was degassed by bubbling argon for 10 min. [b.] Yield is for isomer shown. The minor regioisomers (meta and ortho) were not separated, assigned, or counted for yield. [c.] Yield is the sum of isomers which were separated.

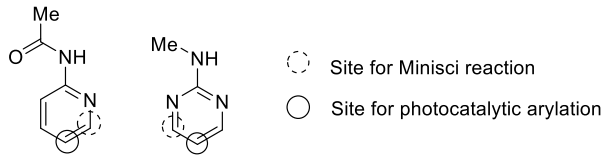
Products **3.6n** and **3.6o** demonstrated the viability of the method to access extended aryl systems, and that even moderately acidic protons are tolerated under the basic reaction conditions. After blocking the C-4 position of 3-chlorotetrafluoropyridine to convert that to an

amide **3.6m'**, the existing 3-Cl was susceptible to photocatalytic arylation (Table 3.6, **3.6m**), allowing access to C-3 arylated product. The comlementary reactivity between S_NAr and photocatalysis which leads to this is depicted in Scheme 3.7 below. Hexafluorobenzene, which is considered as an unactivated perfluoroarene was also engaged in the arylation reaction with moderate yields (**3.6q**).



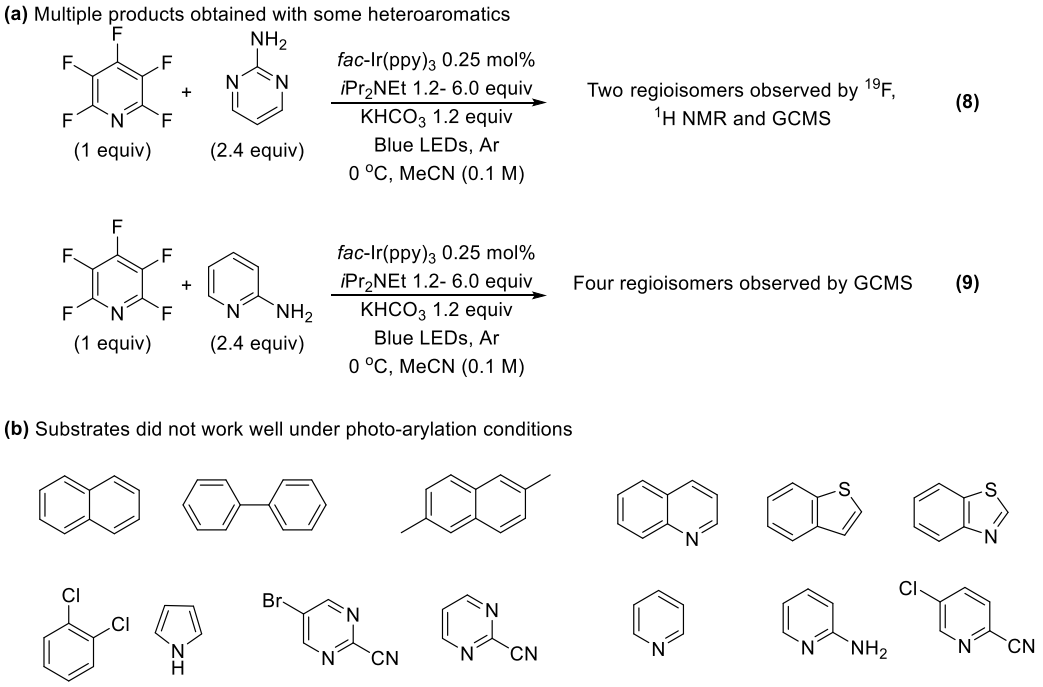
Scheme 3.6 Orthogonal reactivity of S_NAr and photocatalysis

The Minisci reaction is commonly employed to functionalize basic heterocycles by the addition of an aryl or an alkyl radical.[71] The aromatic compound to be functionalized is generally a heteroarene such as pyridine which allows protonation of the N atom.[72] When we performed the photo-arylation reaction using basic heterocycles, *N*-(pyridin-2-yl)acetamide (Table 3.6, **3.6g''**) and *N*-methylpyrimidin-2-amine (**3.6h''**) as arene-H, an unusual selectivity in comparison to the Minisci reaction was observed. Typically radical addition to basic heterocycles such as pyridines and pyrimidines takes place *ortho*- and *para*- to nitrogen within the ring, as a result of protonation at the nitrogen atom.[73] Radical reactions are known to be fastest when the electronics are matched; meaning an electron deficient radicophile reacts faster with a relatively electron rich radical, and vice versa. Since our reaction is under basic conditions, rather than the acidic conditions typical of the Minisci reaction, this polarity reversal is not possible, and results in the observed divergence of the photocatalytic arylation compared to traditional Minisci reaction (Scheme 3.7).



Scheme 3.7 Minisci selectivity *vs.* photocatalytic selectivity on basic heterocycles

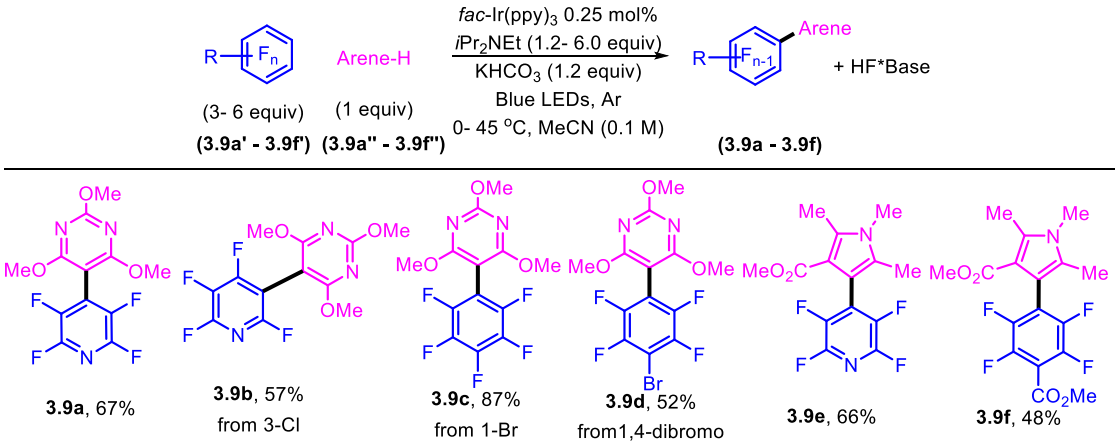
During the screening of substrates, we encountered some regioselectivity issues with respect to the arene-Hs. When the arene-H does not possess a polarizing group, the perfluoroaryl radical addition happened with a diminished selectivity. This can be explained by the stability of the perfluoroaryl radical, which is a highly electron deficient, reactive aryl radical. Correspondingly, the expected transition state (TS) would be early.[27] Since the TS resembles the structure of the nearest intermediate (i.e., the perfluoroaryl radical) and not the product, it is expected to have relatively small barriers to reactivity and consequently the regioselectivity is expected to be diminished. However, this problem was circumvented by substitution or use of polarizing functional groups which biased the addition of the radical to a certain C–H preferentially. For instance, when used as a substrate, 2-aminopyrimidine gave multiple products as shown in Scheme 3.8(a), however, a perfect regioselectivity was achieved after methylation of the amine group to give the product **3.6h** (Scheme 3.6). It is worth noting that there is a possibility of obtaining products with the same molecular mass to the arylated products, simply by an S_NAr reaction between the perfluoroarene and the 2-aminopyrimidine (i.e., *N*-substituted product to the perfluoroarene). Similarly, after acylating 2-aminopyridine the number of regioisomers was reduced from four (Scheme 3.8(a), eq 9) to two regioisomers as shown in the product **3.6g**. Scheme 3.8(b) shows some of the other substrates which display either poor selectivity or give major byproducts.



Scheme 3.8 Substrates that did not work well under photo-arylation conditions

Up to this point our desire was to use the perfluorarene starting material as the limiting reagent. However, an arene-H can also be a valuable coupling partner when a late stage functionalization is considered, especially if the arene-H is prepared *via* a multi-step synthesis. Therefore, we investigated the scenario in which the arene-H is used as the limiting reagent. Given that the mild reaction conditions and its ability to add the perfluoroarenes to sterically congested positions, we envisioned this method could be a way to late stage functionalization of C–H bonds. The reactions were carried out using the standard conditions with superstoicheometric amounts of perfluoroarenes. Meanwhile, excess *i*Pr$_2$NEt was also used since, the reduction was not problematic and in fact, did not affect the yield. We were pleased to see that the reaction was capable of making of fully substituted fluorinated biaryls (Scheme 3.9). Trisubstituted pyrimidines underwent addition to give the C−H coupled product (**3.9a-d**) in good yields. Sterically congested tetrasubstituted pyrroles also coupled with the expected C−F selectivity (**3.9e-f**) to give pentasubstituted pyrroles suggesting that it may be possible to use this

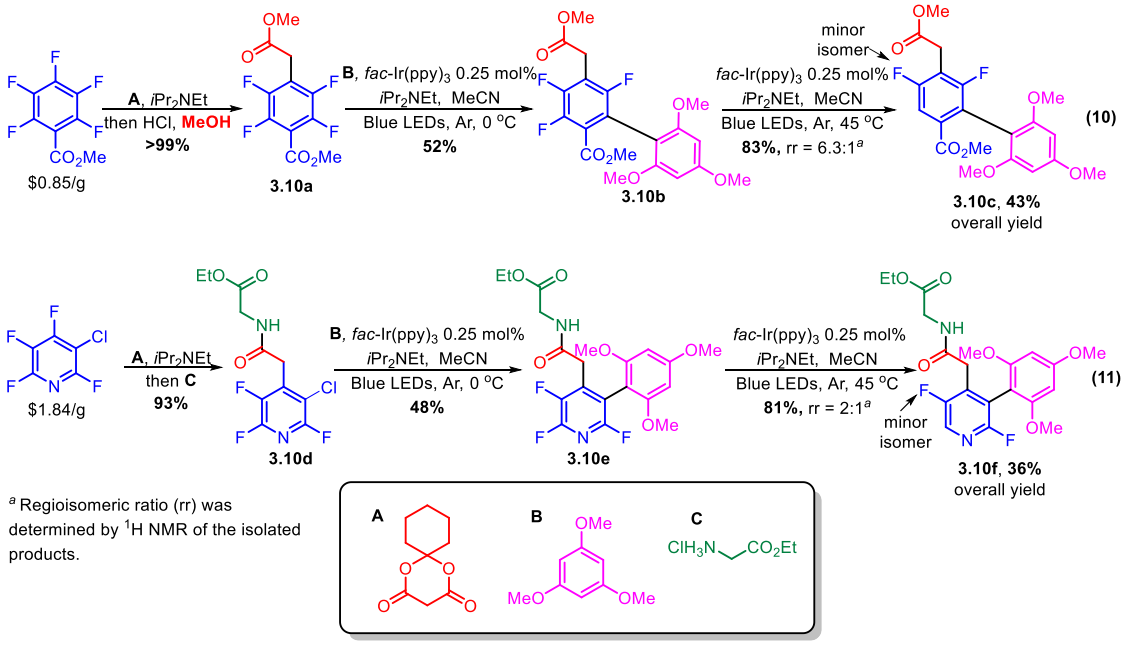
method to accomplish late-stage modifications. Products **3.9b-d** arose from their corresponding C–Cl and C–Br starting materials. The halogen fragmentation pattern we observed was consistent with the radical anion fragmentation observed by Bunnett[74] and Rossi[75] (i.e., I > Br > Cl > F). We utilized this phenomenon to build complementary regioisomers. Subsequent reduction of the C–Br bond was alleviated by simply using the fluorinated arene in excess which gave the product **3.9d**, providing the opportunity for further elaboration by other methods such as traditional cross couplings. In general, the biggest limitation of the method was the use of arene-H compounds that were either highly substituted or polarized, as this reduced the number of isomers that were formed.



Scheme 3.9 Reaction scope with limiting arene-H

Recall, that the ultimate goal of developing C–F functionalization chemistry was to access lightly fluorinated arenes which are extremely valuable but hard to access. Few years ago, our lab demonstrated the ability of achieving this goal by sequential use of S_NAr reactions (will be discussed in chapter IV),[76] photocatalytic C–F alkylation[36b] followed by photo-HDF reaction. S_NAr and C–F alkylation were employed to elaborate parent arenes *via* functionalization and the HDF methodology was employed to further increase the complexity of the final product by reducing the fluorine content. Here we demonstrated the synthesis of functionalized difluoro

arenes starting from commercially available and relatively cheap methyl 2,3,4,5,6-pentafluorobenzoate and 3-chloro-2,4,5,6-tetrafluoropyridine to obtain satisfactory yields over three steps. Specifically, these started with perfluorinated arenes which had all the difficult to install fluorines in the desired positions. Addition of cyclohexyl-Meldrum's acid to the fluoroarene followed by decomposition in the presences of a nucleophile gave near quantitative yields of the product of α-perfluoroarylation (**24a** and **26a**).[77] Photocatalytic arylation was then used to desymmetrize the molecules (**15a** and **14a**). The total fluorine content can then be reduced to multifluorinated benzoates and pyridines that would be otherwise very difficult to synthesize by other methods. The products obtained show the potential of C–F functionalization to be the most rapid and versatile method for accessing multifluorinated arenes which would be useful in discovery chemistry efforts involving fluorinated aromatics.[78]



Scheme 3.10 Elaboration of commercially available aryl fluorides *via* synergistic S_NAr and photocatalysis

3.2 Summary of photocatalytic arylation of per- and polyfluoroarenes

In summary, in this project we have successfully utilized photocatalytically generated perfluoroaryl radical to perform a novel type of C–C bond formation event leading to per(poly)fluoro biaryl products. The process was recognized as the first example of a direct cross-coupling reaction between a C–F bond of one aryl compound and a C–H bond of another aryl compound (dual C–F, C–H functionalization) without having to prefunctionalize either of the aryl coupling partners like in traditional cross-coupling strategies.[79] From a synthetic point of view the reaction has the potential for significant impact given the single step coupling of such broadly accessible coupling partners. The reaction proceeds under mild conditions allowing a good functional group tolerance. From a mechanistic perspective, we showed that the utility of photocatalytically generated perfluoroaryl radical as a versatile coupling partner to intercept with π-systems of a wide range of arenes, including some heteroarenes that give anti-Minisci selectivity, followed by oxidation and rearomatization. Given these initial findings, we expect that this chemistry will facilitate investigation into new fluorinated compounds and therefore enable a number of research efforts.

3.3 Experimental section

General Experimental

All reagents were obtained from commercial suppliers (Sigma-Aldrich, Oakwood chemicals, Alfa Aesar, Matrix Scientific, VWR) and used without further purification unless otherwise noted. Acetonitrile (CH_3CN) was dried over activated molecular sieves. *N*,*N*-diisopropylethylamine was purchased from Oakwood chemicals and was distilled and stored over anhydrous potassium hydroxide. Photocatalysts $Ir(ppy)_3$ [*fac*-tris(2-phenyl pyridinato-C^2, *N*) iridium(III)] and $Ir(CF_3ppy)_3$ [*fac*-tris[2-(4- trifluoromethylphenyl)pyridinato-C^2, *N*)] iridium(III)] were synthesized according to literature procedure (ref- Singh, A.; Teegardin, K.; Kelly, M.;

Prasad, K. S.; Krishnan, S.; Weaver, J. D. *J. Organomet. Chem.* **2015**, *776*, 51). 2-(perfluorophenyl)benzo[*d*]oxazole (ref- Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002.), ethyl 2-(2-(perfluoropyridin-4-yl)acetamido)acetate (ref- Singh, A.; Kubik, J. J.; Weaver, J. D. *Chemical Science* **2015**, *6*, 7206), methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate (ref- Singh, A.; Kubik, J. J.; Weaver, J. D. *Chemical Science* **2015**, *6*, 7206), diethyl 2-(perfluoro-[1,1'-biphenyl]-4-yl)malonate (ref- Senaweera, S. M.; Weaver, J. D. *J. Org. Chem.* **2014**, *79*, 10466), *tert*-butyl 2,3,4,5,6-pentafluorobenzoate (ref- Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002.), 4-amino-2,3,5,6-tetrafluorobenzonitrile (ref- Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002.), *N*-(pyridin-2-yl)acetamide (ref- Kelly, B.; McMullan, M.; Muguruza, C.; Ortega, J. E.; Meana, J. J.; Callado, L. F.; Rozas, I. *J. Med. Chem.* **2015**, *58*, 963), *N*-methylpyrimidin-2-amine (ref- Zidar, N.; Jakopin, Ž.; Madge, D. J.; Chan, F.; Tytgat, J.; Peigneur, S.; Dolenc, M. S.; Tomašić, T.; Ilaš, J.; Mašič, L. P.; Kikelj, D. *European Journal of Medicinal Chemistry* **2014**, *74*, 23), ethyl (2-(perfluoropyridin-4-yl)acetyl)glycinate (ref- Singh, A.; Kubik, J. J.; Weaver, J. D. *Chemical Science* **2015**, *6*, 7206) were synthesized according to literature procedures. Reactions were monitored by ^{19}F NMR and GC-MS (QP 2010S, Shimadzu equipped with auto sampler). NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer or a 400 MHz Unity Inova spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual solvent peak. IR spectra were recorded on a Nicolet iS50 FT-IR. Melting points were determined on a Mel-Temp apparatus and reported uncorrected. Purifications were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica or Sorbtech refillable flash columns (cat. # = FCSTLL-40-12) (4 g, 12 g, 24 g, 40 g) using standard grade silica gel obtained from Sorbent Technologies (cat.# = 30930M-25, 40-63 μm, 230 X 400 mesh) with product detection at 254, 280 nm and by ELSD (evaporative light scattering detector). Some isolations were performed using Sorbent Technology Silica Prep TLC Plates, w/UV254, glass backed, 1000 μm, 20 x 20 cm, and were visualized with ultraviolet light.

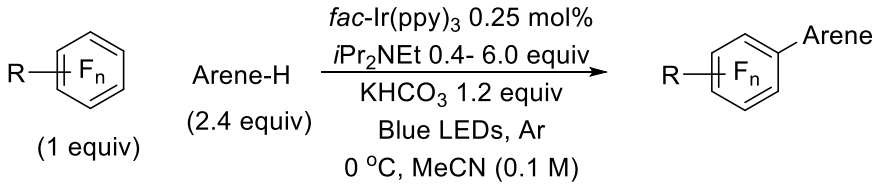
Substrate synthesis reactions were monitored by thin layer chromatography (TLC), obtained from Sorbent Technology Silica XHL TLC Plates, w/UV254, glass backed, 250 μm, and were visualized with ultraviolet light or potassium permanganate.

Photocatalytic Reaction Set up

Photocatalytic reactions were set up in a light bath as described below. Strips of blue LED's (18 LED's/ft.) were purchased from Solid Apollo. The strips (4.9 ft) were wrapped around on the walls of glass crystallization dish and secured with masking tape and then wrapped with aluminum foil. A lid which rest on the top was fashioned from cardboard and holes were made such that NMR tubes were held firmly in the cardboard lid which was placed on the top of the bath. Isopropanol was added to the bath such that the tubes were submerged in isopropanol which was maintained at 0 ^{o}C with the aid of a chiller which circulated coolant through a coil of copper tubing placed in the bath. In some cases the same light bath set up was used with water in it which was maintained at 45 ^{o}C with the aid of a sand bath connected to a thermostat.

Photocatalytic arylation reactions and characterization

General procedure A for the photocatalytic C-F Arylation reaction (with limiting fluoroarene)

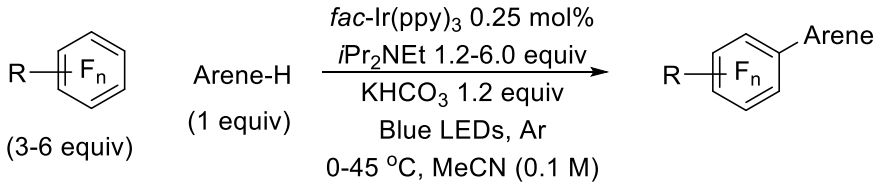


An NMR tube was charged with fluoroarene (0.1 mmol, 1.0 equiv), arene-H (0.24 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (0.04 mmol, 0.4 equiv), *fac*-tris(2- phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.25 mM, 1 mL in MeCN), sealed glass capillary containing C_6D_6 and was capped with an NMR septum (Ace glass, part no. 9096-25). When reaction was run in greater than 0.1 mmol of fluoroarene, more than one NMR tube was used to set up the reaction and each NMR tube had 1 mL of reaction mixture. The reaction was degassed *via* Ar bubbling for 15 min at 0 °C (to avoid evaporation of *N*,*N* diisopropylethylamine and other volatile starting materials) and then placed in a light bath (*vide supra*) such that the lower portion of the tube was submerged under isopropanol (or water). The reaction was monitored periodically by ^{19}F NMR. After the complete consumption of starting material, CH_3CN was removed *via* rotavap. The residue was treated with deionized water (2 mL) and extracted with DCM (3 x 1 mL). The organic portions were combined and dried with anhydrous $MgSO_4$. The combined organic portions were dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by normal phase chromatography.

If the reaction did not go to completion with the first addition of *N*,*N* diisopropylethylamine, an additional 0.2 - 1.2 equiv. of *N*,*N* -diisopropylethylamine was added to

the reaction. Then the reaction was redegassed and returned to the light bath. This sequence was repeated until the reaction reached completion as judged by ^{19}F NMR.

General procedure B for the photocatalytic C-F Arylation reaction (with limiting arene-H)



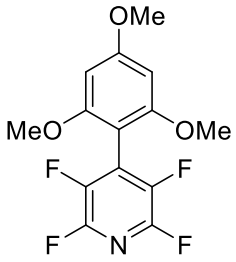
An NMR tube was charged with fluoroarene (0.3 mmol, 3.0 equiv), arene-H (0.1 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (0.12 mmol, 1.2 equiv), *fac*-tris(2- phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.25 mM, 1 mL in MeCN), sealed glass capillary containing C_6D_6 and was capped with NMR septum (Ace glass, part no. 9096-25). When reaction was run in greater than 0.1 mmol of fluoroarene, more than one NMR tube was used to set up the reaction and each NMR tube had 1 mL of reaction mixture. The reaction was degassed *via* Ar bubbling for 15 min at 0 °C (to avoid evaporation of *N*,*N*-diisopropylethylamine and other volatile starting materials) and then placed in a light bath (*vide supra*) such that the lower portion of the tube was submerged under isopropanol (or water). The reaction was monitored periodically by ^{19}F NMR and ^{1}H NMR. After the complete consumption of starting material, the reaction was worked up as described in **General Procedure A**. If the reaction did not go for completion, then, additional increments of *N*,*N*-diisopropylethylamine and $Ir(ppy)_3$ (as necessary) were added to the reaction. Then, the reaction mixture was redegassed and returned to the light bath.

General procedure C for the photocatalytic hydrodefluorination reaction

An NMR tube was charged with fluorinated starting material (0.05 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (0.06 mmol, 1.2 equiv), *fac*-tris(2- phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.25 mM, 0.5 mL in MeCN), sealed glass capillary containing C_6D_6 and

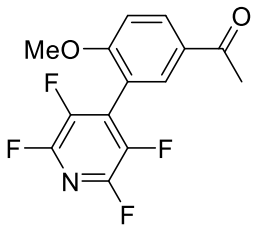
was capped with NMR septum (Ace glass, part no. 9096-25). The reaction was degassed *via* Ar bubbling for 15 min at 0 °C (to avoid evaporation of *N*,*N* diisopropylethylamine and other volatile starting materials) and then placed in a light bath (*vide supra*) such that the lower portion of the tube was submerged under isopropanol (or water). The reaction was monitored periodically by ^{19}F NMR. After the complete consumption of starting material the reaction was worked up as described in **General Procedure A**. If the reaction did not go to completion, then, an additional 1.2 - 2.4 equiv. increment of *N*,*N*-diisopropylethylamine was added to the reaction. Then the reaction was redegassed and returned to the light bath. This sequence was repeated in 20 h intervals until the reaction reached completion as judged by ^{19}F NMR.

Synthesis of 3.6a (2,3,5,6-tetrafluoro-4-(2,4,6-trimethoxyphenyl)pyridine)



The **General procedure A** was followed using pentafluoropyridine (33 µL, 0.3 mmol, 1 equiv), 1,3,5-trimethoxybenzene (121 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (20.9 µL, 0.12 mmol, 0.4 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. The crude material was purified by flash chromatography using hexane : ethyl acetate (0% EtOAc for 5 cv, 0-5% EtOAc for 5-10 cv, 5- 40% EtOAc for 10-17 cv, 45% EtOAc for 17-20 cv and ramped to 100% EtOAc for 20-22 cv and then held at 100% EtOAc for 22-24 cv) on a 12 g silica column to afford **3.6a** in 70% yield (66 mg, 0.21 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.2 – -93.4 (m, 2F), -139.8 – -140.0 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 2H), 3.88 (s, 3H), 3.78 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 158.6, 144.7 – 141.8 (m), 140.3 (dd, *J* = 257.0, 33.4 Hz), 128.2 (tt, *J* = 18.1, 3.6 Hz), 96.1, 90.7, 55.9, 55.5. FT-IR cm^{-1} 1590, 1232, 1123, 922. GC/MS (*m/z*, relative intensity) 317 (M+, 100), 298 (20), 288 (20), 69 (25). mp 118-120 ^{o}C.

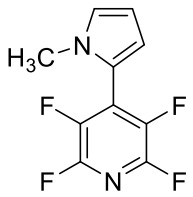
Synthesis of 3.6b (1-(4-methoxy-3-(perfluoropyridin-4-yl)phenyl)ethan-1-one)

The **General procedure A** was followed using pentafluoropyridine (33 µL, 0.3 mmol, 1 equiv),  1-(4-methoxyphenyl)ethan-1-one (108 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (15.6 µL, 0.09 mmol, 0.3 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. Two consecutive additions of 0.2 equiv of *N*,*N*-diisopropylethylamine (7.0 µL) were added after 48 h intervals until the reaction was completed. The crude material was purified by flash chromatography using hexane : ethyl acetate (0% EtOAc for 5 cv, 0-5% EtOAc for 5-25 cv, 5% EtOAc for 25-32 cv, 5-10% EtOAc for 32-40 cv, 10% EtOAc for 40-45 cv and ramped to 100% EtOAc for 45-50 cv and then held at 100% EtOAc for 50-55 cv) on a 24 g silica column to afford **3.6b** in 52% yield (47 mg, 0.16 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.1 – -91.3 (m, 2F), -141.3 – -141.5 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 3.91 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 160.5, 143.6 (dddd, *J* = 244.9, 16.5, 13.2, 2.8 Hz), 141.3 – 138.3 (m), 133.1, 131.8, 130.4, 130.2 (dt, *J* = 16.9, 3.1 Hz), 115.2, 111.2, 56.3, 26.4. FT-IR cm^{-1} 1670, 1459, 1277, 917. GC/MS (*m/z*, relative intensity) 299 (M+, 22), 284 (100), 241 (20). mp 88-90 °C.

Notes:

1. Regiochemistry of the product was determined by a ^{1}H-^{1}H NOESY experiment after irradiation of $–OCH_3$ group and $–COCH_3$ group in two separate experiments. Only the signal at 7.11 ppm was enhanced, after irradiating the $-OCH_3$ group indicating that there was only one aryl C-H in close proximity to the $-OCH_3$ group. Both signals at 7.90 ppm and 8.14 ppm were enhanced, after irradiating the $–COCH_3$ group indicating that there are two aryl C-Hs in close proximity to the $–COCH_3$ group consistent with the structure shown.

Synthesis of 3.6c (2,3,5,6-tetrafluoro-4-(1-methyl-1H-pyrrol-2-yl)pyridine)



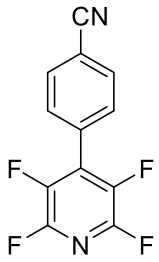
The **General procedure A** was followed using pentafluoropyridine (22 µL, 0.2 mmol, 1 equiv), 1-methyl-1H-pyrrole (40.4 µL, 0.48 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (10.4 µL, 0.06 mmol, 0.3 equiv), $KHCO_3$ (24 mg, 0.24 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.32 mg, 0.0005 mmol, 0.0025 equiv) in CH_3CN was used. An additional 0.3 equiv of *N*,*N*-diisopropylethylamine (10.4 µL) was added after 18 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-2% EtOAc for 2-25 cv and ramped to 100% EtOAc for 25-40 cv and then held at 100% EtOAc for 40-42 cv) on a 12 g silica column to afford **3.6c** in 50% yield (23 mg, 0.10 mmol) as a light brown solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.9 – -91.1 (m, 2F), -142.2 – -142.4 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 3.9 Hz, 1H), 6.51 (d, *J* = 2.7 Hz, 1H), 6.33 (dd, *J* = 3.8, 2.7 Hz, 1H), 3.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (dddd, *J* = 244.6, 17.3, 14.0, 3.0 Hz), 140.6 – 137.1 (m), 127.1, 126.0 (tt, *J* = 15.5, 3.5 Hz), 117.2 (t, *J* = 2.9 Hz), 114.9 (t, *J* = 2.3 Hz), 109.5, 35.2. FT-IR cm^{-1} 1445, 1259, 952. GC/MS (*m/z*, relative intensity) 230 (M+, 100), 209 (10). mp 70-72 °C.

Notes:

1. Due to volatility of compound 1c we did not attempt hard to remove residual solvents.
2. Regiochemistry of the product was determined by a ^{1}H-^{1}H NOESY experiment after irradiation of *N*–CH_3 group. Only the signal at 6.92 ppm was enhanced, indicating that there was only one pyrrole C-H in close proximity consistent with the structure shown.

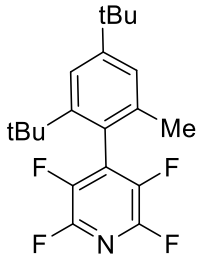
Synthesis of 3.6d (4-(perfluoropyridin-4-yl)benzonitrile)

The **General procedure A** was followed using pentafluoropyridine (55 µL, 0.5 mmol, 1 equiv), benzonitrile (123.7 µL, 1.2 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (43.5 µL, 0.25 mmol,



0.5 equiv), $KHCO_3$ (60 mg, 0.6 mmol, 1.2 equiv) and 5.0 mL of stock solution of $Ir(ppy)_3$ (0.8 mg, 0.00125 mmol, 0.0025 equiv) in CH_3CN was used. An additional 0.2 equiv of *N*,*N*-diisopropylethylamine (17.4 µL) was added after 48 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 3 cv, 0-2% EtOAc for 3-4 cv, 2% EtOAc for 4-15 cv, 2-8% EtOAc for 15-20 cv, 8% EtOAc for 20-23 cv and ramped to 100% EtOAc for 23-28 cv and then held at 100% EtOAc for 28-30 cv) on a 24 g silica column to afford **3.6d** in 58% yield (80 mg, 0.29 mmol). The *para*-substituted product was isolated purely as a white solid and is presented here. The regioisomeric ratio was determined based on the crude NMR. ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.0 – -89.3 (m, 2F), -144.3 – -144.6 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (dd, *J* = 246.1, 14.9 Hz), 140.7 – 137.6 (m), 132.8, 131.7 – 131.2 (m), 130.7, 130.4, 117.9, 114.8. FT-IR cm^{-1} 2236, 1147. GC/MS (*m/z*, relative intensity) 252 (M+, 100), 233 (8). mp 101-102 °C.

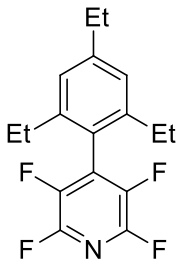
Synthesis of 3.6e (4-(2,4-di-*tert*-butyl-6-methylphenyl)-2,3,5,6-tetrafluoropyridine)



The **General procedure A** was followed using pentafluoropyridine (11 µL, 0.1 mmol, 1 equiv), 1,3-di-*tert*-butyl-5-methylbenzene (49 mg, 0.24 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (8.7 µL, 0.05 mmol, 0.5 equiv), $KHCO_3$ (12 mg, 0.12 mmol, 1.2 equiv) and 1.0 mL of stock solution of $Ir(ppy)_3$ (0.16 mg, 0.00025 mmol, 0.0025 equiv) in CH_3CN was used. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 0-15 cv and ramped to 100% EtOAc for 15-30 cv and then held at 100% EtOAc for 30-32 cv on a 24 g silica column to afford **3.6e** in 35% yield (12 mg, 0.035 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.8 – -91.2 (m, 2F), -138.4 – -138.7 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.9 Hz, 1H), 7.19 (d, *J* = 1.9 Hz, 1H), 1.92 (s, 3H), 1.35 (s, 9H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 148.3, 143.6 (dddd, *J* = 246.2, 16.8, 13.5, 2.9 Hz), 139.7 (ddd, *J* = 254.8, 25.9, 6.4 Hz), 137.2 (t, *J*

= 18.8 Hz), 135.5, 125.2, 122.6, 120.5, 36.4, 34.8, 31.8, 31.3, 21.1. FT-IR cm^{-1} 1103, 909. GC/MS (*m/z*, relative intensity) 353 (M+, 17), 338 (100), 57 (70). mp 96-98 °C.

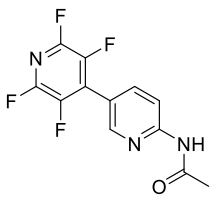
Synthesis of 3.6f (2,3,5,6-tetrafluoro-4-(2,4,6-triethylphenyl)pyridine



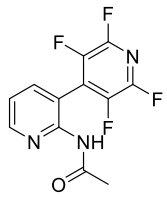
The **General procedure A** was followed using pentafluoropyridine (22 µL, 0.2 mmol, 1 equiv), *N*-methylpyrimidin-2-amine (52.4 mg, 0.48 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol, 0.2 equiv), $KHCO_3$ (24 mg, 0.24 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.32 mg, 0.0005 mmol, 0.0025 equiv) in CH_3CN was used. Two consecutive additions of 0.2 equiv of *N*,*N*-diisopropylethylamine (7.0 µL) were added after 36 h intervals until the reaction was completed. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 10 cv, 0-4% EtOAc for 10-12 cv, 4-8% EtOAc for 12-20 cv and ramped to 100% EtOAc for 20-23 cv and then held at 100% EtOAc for 23-25 cv on a 24 g silica column to afford **3.6f** in 55% yield (36 mg, 0.11 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.6 – -90.8 (m, 2F), -140.5 – -140.7 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 2H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.33 (q, *J* = 7.6 Hz, 4H), 1.31 (t, *J* = 7.6 Hz, 3H), 1.09 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 143.6 (dt, *J* = 246.5, 16.2 Hz), 142.2, 139.6 (ddd, *J* = 255.6, 25.9, 6.0 Hz), 133.7 (t, *J* = 19.0 Hz), 125.9, 120.9, 28.8, 26.8, 15.2, 14.9. FT-IR cm^{-1} 1120, 873. GC/MS (*m/z*, relative intensity) 311 (M+, 98), 296 (60), 282 (100).

Synthesis of 3.6g-i (*N*-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-6-yl)acetamide) and 3.6g-ii (*N*-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-2-yl)acetamide)

The **General procedure A** was followed using pentafluoropyridine (33 µL, 0.3 mmol, 1 equiv), *N*-(pyridin-2-yl)acetamide (97.9 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (21 µL, 0.12 mmol, 0.4 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. An additional 0.3 equiv of



7a-i

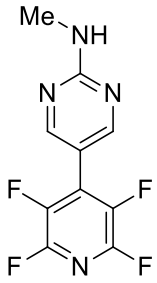


7a-ii

N,*N*-diisopropylethylamine (15.6 µL) was added after 36 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-40% EtOAc for 2-10 cv, 40% EtOAc for 10-20 cv and ramped to 100% EtOAc for 20-25 cv and then held at 100% EtOAc for 25-27 cv on a 24 g silica column to afford **3.6g-i** in 35% yield (30 mg, 0.11 mmol) as a yellow solid. Remaining fractions after the column was collected and concentrated and purified using a prep-TLC (hexane: ethyl acetate-40:60) to afford **3.6g-ii** in 35% yield (30 mg, 0.11 mmol) as a white solid. **3.6g-i** ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.7 – -89.9 (m, 2F), -144.9 – -145.1 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.25 (br s, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 152.8, 148.6, 144.2 (dt, *J* = 247.8, 15.0 Hz), 139.9, 139.3 (ddd, *J* = 259.7, 27.9, 6.5 Hz), 129.9 (t, *J* = 14.7 Hz), 118.3, 113.9, 24.9. FT-IR cm^{-1} 3253, 1701, 1589, 1227. GC/MS (*m/z*, relative intensity) 285 (M+, 10), 243 (45), 216 (40), 48 (100). mp 150-152 °C. **3.6g-ii** ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.5 (br s, 2F), -143.1 (br s, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.9 Hz, 1H), 8.49 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.36 (dd, *J* = 7.8, 4.7 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 150.2, 148.7, 145.3 – 142.1 (m), 140.5, 140.5 – 137.3 (m), 131.8 (dd, *J* = 19.0, 8.8 Hz), 121.3, 117.0, 23.7. FT-IR cm^{-1} 3166, 1692, 1533, 1219. GC/MS (*m/z*, relative intensity) 285 (M+, 5), 243 (35), 223 (40). mp 146-147 °C.

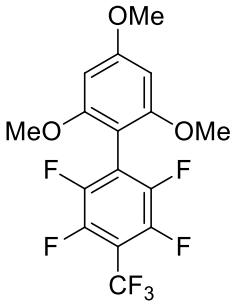
Note: The regiochemistry was assigned based on reference coupling constants for pyridine systems and expected ^{13}C shifts. Our attempt to assign the regiochemistry using ^{1}H-^{1}H NOESY was not successful. After irradiation of methyl group in the acetyl functionality (500 ms mixing time) did not show any correlation with aromatic-Hs. Irradiation of N-H did not show any correlation with aromatic-Hs presumably, due to fast exchange with the solvent.

Synthesis of 3.6h (*N*-methyl-5-(perfluoropyridin-4-yl)pyrimidin-2-amine)



The **General procedure A** was followed using pentafluoropyridine (22 µL, 0.2 mmol, 1 equiv), *N*-methylpyrimidin-2-amine (52.4 mg, 0.48 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (17.4 µL, 0.1 mmol, 0.5 equiv), $KHCO_3$ (24 mg, 0.24 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.32 mg, 0.0005 mmol, 0.0025 equiv) in CH_3CN was used. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 3 cv, 0-35% EtOAc for 3-8 cv, 35% EtOAc for 8-13 cv, 35-85% EtOAc for 13-15 cv, 85% EtOAc for 15-22 cv and ramped to 100% EtOAc for 22-23 cv and then held at 100% EtOAc for 23-25 cv on a 24 g silica column to afford **3.6h** in 57% yield (29 mg, 0.11 mmol) as an off-white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.2 – -90.4 (m, 2F), -145.4 – -145.6 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 2H), 5.84 (s, 1H), 3.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 158.8, 144.3 (dddd, J = 245.1, 17.1, 13.8, 2.8 Hz), 140.6 – 137.5 (m), 128.6 (tt, J = 14.3, 3.0 Hz), 109.9, 28.5. FT-IR cm^{-1} 3264, 1597, 1166, 945. GC/MS (*m/z*, relative intensity) 258 (M+, 100), 230 (35), 210 (30). mp 162-163 °C.

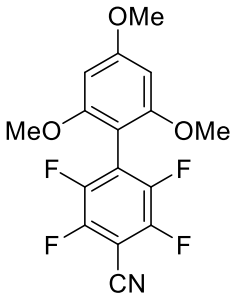
Synthesis of 3.6i (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-4-(trifluoromethyl)-1,1'-biphenyl)



The **General procedure A** was followed using 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)benzene (42.3 µL, 0.3 mmol, 1 equiv), 1,3,5-trimethoxybenzene (121 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (15.6 µL, 0.04 mmol, 0.3 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. An additional 0.2 equiv of *N*,*N*-diisopropylethylamine (10.4 µL) was added after 20 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 5 cv, 0-5% EtOAc for 5-10 cv, 5% EtOAc for 10-20 cv and ramped to 100% EtOAc for 20-30 cv and then held at 100% EtOAc for

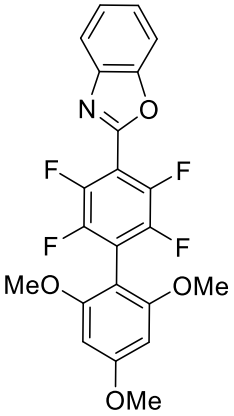
30-32 cv on a 24 g silica column to afford **3.6i** in 54% yield (62 mg, 0.16 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.2 (t, *J* = 21.7 Hz, 3F), -136.7 – -136.8 (m, 2F), -142.8 – -143.2 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 2H), 3.88 (s, 3H), 3.78 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 158.8, 146.5 – 143.2 (m), 143.8 (dd, *J* = 258.2, 17.6 Hz), 119.0 (t, *J* = 19.5 Hz), 107.9 (dt, *J* = 33.7, 12.6 Hz), 103.5, 96.2, 90.7, 55.9, 55.4. FT-IR cm^{-1} 1207, 1128, 920. GC/MS (*m/z*, relative intensity) 384 (M+, 100), 365 (30), 355 (20), 69 (20). mp 127-128 °C.

Synthesis of 3.6j (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carbonitrile)



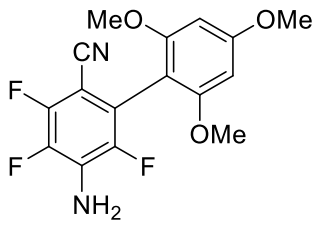
The **General procedure A** was followed using 2,3,4,5,6-pentafluorobenzonitrile (37.8 µL, 0.09 mmol, 1 equiv), 1,3,5-trimethoxybenzene (121 mg, 0.72 mmol, 2.4 equiv), *N,N*-diisopropylethylamine (15.6 µL, 0.04 mmol, 0.3 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. An additional 0.5 equiv of *N,N*-diisopropylethylamine (26 µL) was added after 36 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-12% EtOAc for 2-6 cv, 12% EtOAc for 6-13 cv, 12-85% EtOAc for 13-20 cv, 85% EtOAc for 20-22 cv and ramped to 100% EtOAc for 22-24 cv and then held at 100% EtOAc for 24-26 cv on a 24 g silica column to afford **3.6j** in 57% yield (58 mg, 0.17 mmol) as an off-white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.7 – -134.9 (m, 2F), -135.1 – -135.3 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 2H), 3.88 (s, 3H), 3.77 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 158.8, 147.1 (ddt, *J* = 243.2, 21.3, 5.1 Hz), 145.7 – 143.3 (m), 121.9 (t, *J* = 18.6 Hz), 108.3 (t, *J* = 3.7 Hz), 95.9, 92.4 (t, *J* = 16.9 Hz), 90.8, 56.0, 55.6. FT-IR cm^{-1} 2240, 1589, 1128, 807. GC/MS (*m/z*, relative intensity) 341 (M+, 100), 312 (25), 69 (25). mp 112-113 °C.

Synthesis of 3.6k (2-(2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-yl)benzo[d]oxazole)



The **General procedure A** was followed using 2-(perfluorophenyl)benzo[*d*]oxazole (57.0 mg, 0.2 mmol, 1 equiv), 1,3,5-trimethoxybenzene (80.6 mg, 0.48 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (17.4 µL, 0.10 mmol, 0.5 equiv), $KHCO_3$ (24 mg, 0.24 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.32 mg, 0.0005 mmol, 0.0025 equiv) in CH_3CN was used. An additional 0.3 equiv of *N*,*N*-diisopropylethylamine (10.4 µL) was added after 60 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-8% EtOAc for 2-8 cv, 8% EtOAc for 8-12 cv, 8-18% EtOAc for 12-17 cv, 18% EtOAc for 17-22 cv and ramped to 100% EtOAc for 22-28 cv and then held at 100% EtOAc for 28-30 cv on a 24 g silica column to afford **3.6k** in 52% yield (45 mg, 0.10 mmol) as an off-white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.5 – -137.8 (m, 2F), -140.0 – -140.3 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.39 (m, 2H), 6.25 (s, 2H), 3.88 (s, 3H), 3.80 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 158.9, 153.9 (t, *J* = 3.9 Hz), 150.5, 146.6 – 143.3 (m), 146.2 – 143.4 (m), 141.3, 126.2, 125.0, 120.8, 117.8 (t, *J* = 19.4 Hz), 111.0, 106.4 (t, *J* = 13.5 Hz), 96.8, 90.7, 55.9, 55.5. FT-IR cm^{-1} 1591, 1123. GC/MS (*m/z*, relative intensity) 433 (M+, 90), 64 (100). mp 184-187 °C.

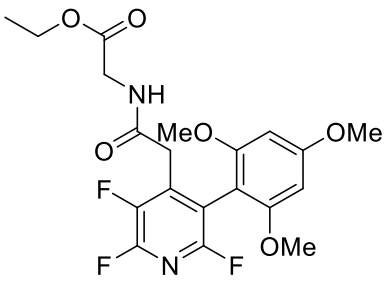
Synthesis of 3.6l (5-amino-3,4,6-trifluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-2-carbonitrile)



The **General procedure A** was followed using 4-amino-2,3,5,6-tetrafluorobenzonitrile (57.0 mg, 0.3 mmol, 1 equiv), 1,3,5-trimethoxybenzene (121.0 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (26.1 µL, 0.15 mmol, 0.5 equiv), $KHCO_3$

(36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. Two consecutive additions of 1.2 equiv of *N*,*N*-diisopropylethylamine (21 µL) were added after 20 h intervals until the reaction was completed. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-7% EtOAc for 2-8 cv, 7% EtOAc for 8-9 cv, 7-11% EtOAc for 9-12 cv, 11% EtOAc for 12-15 cv, 11-38% EtOAc for 15-17 cv, 38% EtOAc for 17-22 cv and ramped to 100% EtOAc for 22-24 cv and then held at 100% EtOAc for 24-26 cv on a 24 g silica column to afford **3.6l** in 53% yield (53 mg, 0.16 mmol) as a light yellow solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.2 (t, *J* = 11.6 Hz, 1F), -136.5 (dd, *J* = 20.5, 11.0 Hz, 1F), -156.9 (dd, *J* = 20.6, 12.2 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 2H), 4.38 (s, 2H), 3.85 (s, 3H), 3.77 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 158.7, 149.3 (ddd, *J* = 253.5, 12.2, 2.9 Hz), 144.7 (ddd, *J* = 237.4, 6.4, 2.1 Hz), 138.0 (ddd, *J* = 241.6, 15.1, 7.5 Hz), 130.7 (ddd, *J* = 18.8, 12.3, 4.0 Hz), 121.6 (dd, *J* = 19.9, 3.2 Hz), 113.4 (t, *J* = 3.9 Hz), 100.7, 91.4 (dd, *J* = 12.7, 6.5 Hz), 90.9, 55.9, 55.5. FT-IR cm^{-1} 3445, 3342, 2226, 1584, 1123. GC/MS (*m/z*, relative intensity) 338 (M+, 100), 323 (10), 69 (20). mp 188-190 °C.

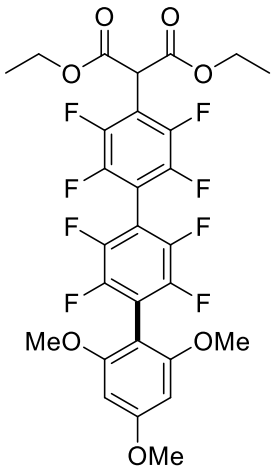
Synthesis of 3.6m (ethyl (2-(2,3,6-trifluoro-5-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)



The **General procedure A** was followed using ethyl (2-(perfluoropyridin-4-yl)acetyl)glycinate (93.0 mg, 0.3 mmol, 1 equiv), 1,3,5-trimethoxybenzene (121.0 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (62.6 µL, 0.36 mmol, 1.2 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. Two consecutive additions of 0.5 equiv of *N*,*N*-diisopropylethylamine (26.1 µL) were added after 36 h intervals until the reaction was completed. The crude material was purified by flash

chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-40% EtOAc for 2-15 cv, 40% EtOAc for 15-25 cv and ramped to 100% EtOAc for 25-30 cv and then held at 100% EtOAc for 30-32 cv on a 24 g silica column to afford **3.6m** in 48% yield (66 mg, 0.14 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.7 (dd, *J* = 27.0, 12.6 Hz, 1F), -90.5 (dd, *J* = 23.0, 12.6 Hz, 1F), -147.3 (dd, *J* = 26.7, 23.4 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.96 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.90 (d, *J* = 5.1 Hz, 2H), 3.85 (s, 3H), 3.70 (s, 6H), 3.51 (d, *J* = 1.9 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 167.2, 162.8, 158.6, 153.3 (dd, *J* = 242.0, 12.0 Hz), 149.5 – 146.5 (m), 141.7 (ddd, *J* = 253.6, 25.3, 5.9 Hz), 140.0 (dt, *J* = 12.4, 3.9 Hz), 115.3 (dd, *J* = 33.7, 6.4 Hz), 99.8 (d, *J* = 3.4 Hz), 90.8, 61.5, 55.8, 55.5, 41.6, 35.0, 14.1. FT-IR cm^{-1} 3376, 1731, 1585, 1127. GC/MS (*m/z*, relative intensity) 442 (M+, 80), 297 (10), 240 (55), 281 (100). mp 158-161 °C.

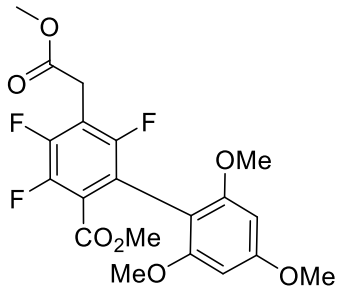
Synthesis of 3.6n (diethyl 2-(2,2',3,3',5,5',6,6'-octafluoro-2'',4'',6''-trimethoxy-[1,1':4',1''-terphenyl]-4-yl)malonate)



The **General procedure A** was followed using diethyl 2-(perfluoro-[1,1'-biphenyl]-4-yl)malonate (94.8 mg, 0.2 mmol, 1 equiv), 1,3,5-trimethoxybenzene (80.6 mg, 0.48 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (10.4 µL, 0.06 mmol, 0.3 equiv), $KHCO_3$ (24 mg, 0.24 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.32 mg, 0.0005 mmol, 0.0025 equiv) in CH_3CN was used. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-5% EtOAc for 2-5 cv, 5% EtOAc for 5-12 cv, 5-35% EtOAc for 12-18cv, 35% EtOAc for 18-23 cv and ramped to 100% EtOAc for 23-35 cv and then held at 100% EtOAc for 25-27 cv on a 40 g silica column to afford **3.6** in 50% yield (62 mg, 0.10 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.7 – -137.8 (m, 2F), -137.9 – -138.1 (m, 2F), -139.9 – -140.1 (m, 2F), -140.4 (dd, *J* = 20.7, 9.7 Hz, 2F). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 6.25 (s, 2H), 5.08 (s, 1H), 4.33 (q, *J* = 6.6 Hz, 4H), 3.88 (s, 3H), 3.80 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 163.1, 158.9, 146.6 – 145.8 (m), 145.2 (ddt, *J* = 39.9, 15.7, 3.9 Hz), 144.1 – 143.4 (m), 142.7 (ddt, *J* = 36.9, 15.8, 4.4 Hz), 116.7 (t, *J* = 19.3 Hz), 114.6 (t, *J* = 16.7 Hz), 108.3 (t, *J* = 18.5 Hz), 105.0 (t, *J* = 18.2 Hz), 96.9, 90.7, 62.8, 55.9, 55.4, 47.7, 13.9. FT-IR cm^{-1} 1749, 1590, 1129. GC/MS (*m/z*, relative intensity) 550 ((M-CO_2Et)+, 100)), 477 (40), 69 (20). mp 144-147 °C.

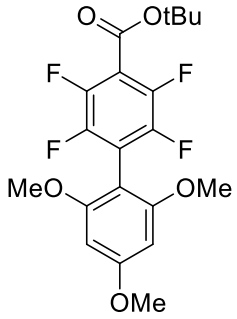
Synthesis of 3.6o (methyl 3,4,6-trifluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)



The **General procedure A** was followed using methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate (84.0 mg, 0.3 mmol, 1 equiv), 1,3,5-trimethoxybenzene (121.0 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (26.1 µL, 0.15 mmol, 0.5 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. An additional 0.5 equiv of *N*,*N*-diisopropylethylamine (26.1 µL) was added after 36 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 5 cv, 0-12% EtOAc for 5-10 cv, 12% EtOAc for 10-13 cv, 12-45% EtOAc for 13-20 cv, 45% EtOAc for 20-24 cv and ramped to 100% EtOAc for 24-27 cv and then held at 100% EtOAc for 27-30 cv on a 24 g silica column to afford **3.6o** in 52% yield (66 mg, 0.15 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.9 (dd, *J* = 14.5, 3.6 Hz, 1F), -137.9 (dd, *J* = 22.0, 3.6 Hz, 1F), -143.6 (dd, *J* = 22.0, 14.5 Hz, 1F). ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (s, 2H), 3.83 (s, 3H), 3.77 (s, 2H), 3.72 (s, 3H), 3.70 (s, 6H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 163.7 (t, *J* = 3.4 Hz), 162.0, 158.4, 154.1 (ddd, *J* = 245.0, 5.7, 2.8 Hz), 148.2 (ddd, *J* = 250.0, 15.0, 8.3 Hz), 145.0 (ddd, *J* = 251.2, 14.5, 3.9 Hz), 123.1 (dd, *J* = 12.3, 4.4 Hz), 117.7 (dd, *J* = 21.5, 4.8 Hz), 114.0 (dd, *J* = 24.1, 16.3 Hz), 102.1, 90.6, 55.8, 55.3, 52.5, 52.3, 28.5. FT-IR cm^{-1} 1736, 1587,

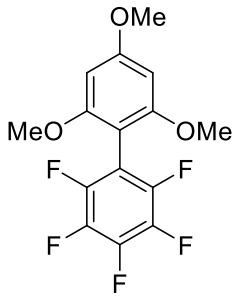
1125. GC/MS (*m/z*, relative intensity) 428 (M+, 100), 297 (15), 275 (30), 59 (50). mp 110-112 ^{o}C.

Synthesis of 3.6p (*tert*-butyl 2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carboxylate)



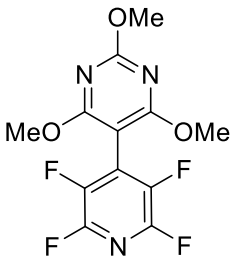
The **General procedure A** was followed using *tert*-butyl 2,3,4,5,6-pentafluorobenzoate (107.2 mg, 0.4 mmol, 1 equiv), 1,3,5-trimethoxybenzene (161.3 mg, 0.96 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (21 µL, 0.12 mmol, 0.3 equiv), $KHCO_3$ (48 mg, 0.48 mmol, 1.2 equiv) and 4.0 mL of stock solution of $Ir(ppy)_3$ (0.66 mg, 0.001 mmol, 0.0025 equiv) in CH_3CN was used. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-10% EtOAc for 2-8 cv, 10% EtOAc for 8-15 cv, 10-15% EtOAc for 15-17 cv, 15% EtOAc for 17-20 cv and ramped to 100% EtOAc for 22-25 cv and then held at 100% EtOAc for 25-27 cv on a 24 g silica column to afford **3.6p** in 58% yield (97 mg, 0.23 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -138.3 – -138.4 (m, 2F), -143.1 – -143.3 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 2H), 3.85 (s, 3H), 3.75 (s, 6H), 1.62 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 159.3, 158.9, 145.7 (ddt, *J* = 57.5, 16.0, 4.8 Hz), 143.2 (ddt, *J* = 63.5, 16.2, 5.1 Hz), 116.9 (t, *J* = 19.6 Hz), 113.0 (t, *J* = 16.9 Hz), 96.9, 90.8, 84.3, 55.9, 55.5, 28.2. FT-IR cm^{-1} 1730, 1579, 1129. GC/MS (*m/z*, relative intensity) 316 (M-CO_2tBu)+, 100), 297 (20), 287 (50). mp 102-104 ^{o}C.

Synthesis of 3.6q (2,3,4,5,6-pentafluoro-2',4',6'-trimethoxy-1,1'-biphenyl)



The **General procedure A** was followed using perfluorobenzene (34.5 µL, 0.3 mmol, 1 equiv), 1,3,5-trimethoxybenzene (121.0 mg, 0.72 mmol, 2.4 equiv), *N*,*N*-diisopropylethylamine (62.6 µL, 0.36 mmol, 1.2 equiv), $KHCO_3$ (36 mg, 0.36 mmol, 1.2 equiv) and 3.0 mL of stock solution of $Ir(ppy)_3$ (0.48 mg, 0.00075 mmol, 0.0025 equiv) in CH_3CN was used. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 3 cv, 0-5% EtOAc for 3-12 cv, 5% EtOAc for 12-20 cv and ramped to 100% EtOAc for 20-32 cv and then held at 100% EtOAc for 32-35 cv on a 40 g silica column to afford **3.6q** in 50% yield (50 mg, 0.15 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -138.7 – -138.9 (m, 2F), -157.2 (t, *J* = 20.9 Hz, 1F), -164.0 – -164.4 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 2H), 3.87 (s, 3H), 3.76 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 158.9, 146.2 – 143.4 (m), 141.8 – 138.8 (m), 138.9 – 136.0 (m), 109.1 (td, *J* = 19.8, 3.8 Hz), 96.3, 90.7, 55.9, 55.4. FT-IR cm^{-1} 1584, 1126. GC/MS (*m/z*, relative intensity) 334 (M+, 100), 305 (35), 291 (20). mp 121-123 °C.

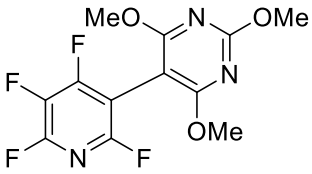
Synthesis of 3.9a (2,4,6-trimethoxy-5-(perfluoropyridin-4-yl)pyrimidine)



The **General procedure B** was followed using pentafluoropyridine (66 µL, 0.6 mmol, 3 equiv), 2,4,6-trimethoxypyrimidine (34.0 mg, 0.2 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (41.7 µL, 0.24 mmol, 1.2 equiv), $KHCO_3$ (24 mg, 0.24 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.32 mg, 0.0005 mmol, 0.0025 equiv) in CH_3CN was used. This reaction was carried out at 45 °C. Two consecutive additions of 0.8 equiv of *N*,*N*-diisopropylethylamine (27.8 µL) were added after 20 h intervals. After complete consumption of fluorinated starting material another 3 equiv of pentafluoropyridine (66 µL), 0.0025 equiv of $Ir(ppy)_3$ (0.48 mg), 1.2 equiv of *N*,*N*-diisopropylethylamine (41.7 µL) was added and degassed

followed by another addition of *N,N*-diisopropylethylamine (41.7 µL) after 24 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 10 cv, 0-2% EtOAc for 10-12 cv, 2% EtOAc for 12-30 cv, 2-8% EtOAc for 30-40 cv, 8% EtOAc for 40-50 cv and ramped to 100% EtOAc for 50-52 cv and then held at 100% EtOAc for 52-55 cv on a 12 g silica column to afford **3.9a** in 67% yield (43 mg, 0.13 mmol) as a yellow solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.9 – -92.2 (m, 2F), -138.8 – -139.1 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3H), 3.97 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 165.9, 143.3 (dddd, *J* = 244.0, 16.8, 13.6, 2.8 Hz), 141.6 – 138.5 (m), 125.5 (tt, *J* = 16.9, 3.3 Hz), 84.2, 55.1, 54.8. FT-IR cm^{-1} 1596, 1129. GC/MS (*m/z*, relative intensity) 319 (M+, 75), 300 (100), 274 (20). mp 98-101 °C.

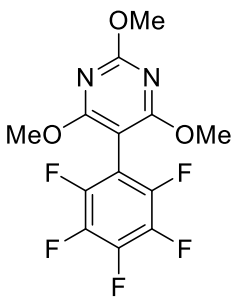
Synthesis of 3.9b (2,4,6-trimethoxy-5-(perfluoropyridin-3-yl)pyrimidine)



The **General procedure B** was followed using 3-chloro-2,4,5,6-tetrafluoropyridine (138.3 µL, 1.2 mmol, 3 equiv), 2,4,6-trimethoxypyrimidine (68.1 mg, 0.4 mmol, 1 equiv), *N,N*-diisopropylethylamine (83.5 µL, 0.48 mmol, 1.2 equiv), $KHCO_3$ (48 mg, 0.48 mmol, 1.2 equiv) and 4.0 mL of stock solution of $Ir(ppy)_3$ (0.66 mg, 0.001 mmol, 0.0025 equiv) in CH_3CN was used. This reaction was carried out at 0 °C. Two consecutive additions of 1.2 equiv of *N,N*-diisopropylethylamine (83.5 µL) were added after 20 h intervals. After complete consumption of fluorinated starting material another 3 equiv of 3-chloro-2,4,5,6-tetrafluoropyridine (138.2 µL), 0.0025 equiv of $Ir(ppy)_3$ (0.66 mg), 1.2 equiv of *N,N*-diisopropylethylamine (83.5 µL) was added and degassed followed by another addition of *N,N*-diisopropylethylamine (83.5 µL) after 24 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 3 cv, 0-25% EtOAc for 3-30 cv, 25% EtOAc for 30-35 cv and ramped to 100% EtOAc for 35-50 cv and then held at 100% EtOAc for 50-55 cv on a 24 g silica column to afford **3.9b** in 57% yield (81 mg, 0.23 mmol) as a light brown solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.7 (dt, *J* = 23.8, 13.7 Hz), -85.9 (ddd, *J* = 22.8, 18.7, 14.0 Hz), -111.8 (td, *J* = 19.6, 13.2 Hz), -167.5 (q, *J* =

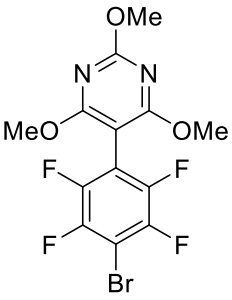
22.1 Hz). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 3.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 165.5, 158.1 (ddd, *J* = 264.9, 15.7, 9.6 Hz), 153.0 (dddd, *J* = 244.2, 14.4, 9.9, 2.4 Hz), 149.2 (dtd, *J* = 243.8, 12.1, 11.1, 7.2 Hz), 133.1 (dddd, *J* = 258.6, 29.0, 15.0, 7.8 Hz), 103.3 (dddd, *J* = 37.2, 17.3, 7.1, 2.1 Hz), 84.0 (d, *J* = 4.0 Hz), 55.2, 54.8. FT-IR cm^{-1} 1591, 1130. GC/MS (*m/z*, relative intensity) 319 (M+, 100), 300 (100), 274 (25), 70 (80). mp 78-79 °C.

Synthesis of 3.9c (2,4,6-trimethoxy-5-(perfluorophenyl)pyrimidine)



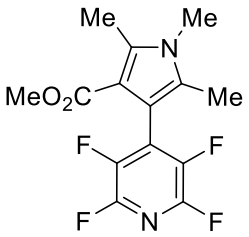
The **General procedure B** was followed using 1-bromo-2,3,4,5,6-pentafluorobenzene (148 µL, 1.2 mmol, 3 equiv), 2,4,6-trimethoxypyrimidine (68.1 mg, 0.4 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (83.5 µL, 0.48 mmol, 1.2 equiv), $KHCO_3$ (48 mg, 0.48 mmol, 1.2 equiv) and 4.0 mL of stock solution of $Ir(ppy)_3$ (0.66 mg, 0.001 mmol, 0.0025 equiv) in CH_3CN was used. This reaction was carried out at 0 °C. Two consecutive additions of 1.2 equiv of *N*,*N*-diisopropylethylamine (83.5 µL) were done after 20 h intervals. After complete consumption of fluorinated starting material another 3 equiv of 1-bromo-2,3,4,5,6-pentafluorobenzene (148 µL), 0.0025 equiv of $Ir(ppy)_3$ (0.66 mg), 1.2 equiv of *N*,*N*-diisopropylethylamine (83.5 µL) was added and degassed followed by another addition of *N*,*N*-diisopropylethylamine (83.5 µL) after 24 h. The crude material was purified by flash chromatography using hexane: DCM (0% DCM for 2 cv, 0-40% DCM for 2-20 cv, 40% DCM for 20-24 cv and ramped to 100% DCM for 24-26 cv and then held at 100% DCM for 26-28 cv on a 24 g silica column to afford **3.9c** in 87% yield (116 mg, 0.35 mmol) as a light yellow solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.8 – -138.0 (m, 2F), -155.4 (t, *J* = 20.9 Hz, 1F), -163.1 – -163.3 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H), 3.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 165.4, 146.3 – 143.4 (m), 142.5 – 139.5 (m), 139.2 – 136.0 (m), 106.7 (td, *J* = 19.1, 3.5 Hz), 84.3, 55.1, 54.7. FT-IR cm^{-1} 1596, 1130. GC/MS (*m/z*, relative intensity) 336 (M+, 90), 317 (100), 291 (20), 70 (48). mp 110-111 °C.

Synthesis of 3.9d (5-(4-bromo-2,3,5,6-tetrafluorophenyl)-2,4,6-trimethoxypyrimidine)



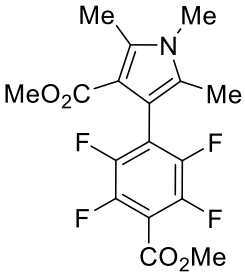
The **General procedure B** was followed using 1,4-dibromo-2,3,5,6-tetrafluorobenzene (369.5 mg, 1.2 mmol, 3 equiv), 2,4,6-trimethoxypyrimidine (68.1 mg, 0.4 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (83.5 µL, 0.48 mmol, 1.2 equiv), $KHCO_3$ (48 mg, 0.48 mmol, 1.2 equiv) and 4.0 mL of stock solution of $Ir(ppy)_3$ (0.66 mg, 0.001 mmol, 0.0025 equiv) in CH_3CN was used. This reaction was carried out at 0 °C. Two consecutive additions of 1.2 equiv of *N*,*N*-diisopropylethylamine (83.5 µL) were done after 20 h intervals. The crude material was purified by flash chromatography using hexane: DCM (0% DCM for 2 cv, 0-55% DCM for 2-15 cv, 55% DCM for 15-20 cv and ramped to 100% DCM for 20-22 cv and then held at 100% DCM for 22-25 cv on a 24 g silica column to afford **3.9d** in 52% yield (83 mg, 0.21 mmol) as a light yellow solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.4 – -134.6 (m, 2F), -136.7 – -136.8 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H), 3.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 165.4, 146.4 – 143.1 (m), 146.4 – 143.4 (m), 111.4 (t, J = 19.0 Hz), 99.3 (t, J = 22.6 Hz), 84.9, 55.1, 54.7 (d, J = 1.5 Hz). FT-IR cm^{-1} 1598, 1128. GC/MS (*m/z*, relative intensity) 398 (M+, 75), 377 (45), 317 (100), 70 (65). mp 124-125 °C.

Synthesis of 3.9e (methyl 1,2,5-trimethyl-4-(perfluoropyridin-4-yl)-1H-pyrrole-3-carboxylate)



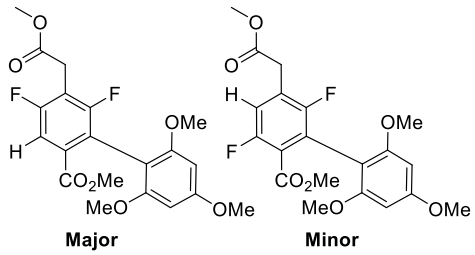
The **General procedure B** was followed using pentafluoropyridine (33 µL, 0.3 mmol, 3 equiv), methyl 1,2,5-trimethyl-1H-pyrrole-3-carboxylate (16.7 mg, 0.1 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (3.5 µL, 0.02 mmol, 0.2 equiv), $KHCO_3$ (12 mg, 0.12 mmol, 1.2 equiv) and 1.0 mL of stock solution of $Ir(ppy)_3$ (0.16 mg, 0.00025 mmol, 0.0025 equiv) in CH_3CN was used. This reaction was carried out at 45 °C. Two consecutive additions of 0.5 equiv of *N*,*N*-diisopropylethylamine (8.7 µL) were done after 20 h intervals. After complete consumption of fluorinated starting material another 2 equiv of pentafluoropyridine (22 µL), 0.0025 equiv of $Ir(ppy)_3$ (0.16 mg), 0.5 equiv of *N*,*N*-diisopropylethylamine (8.7 µL) was added and degassed followed by another addition of *N*,*N*-diisopropylethylamine (8.7 µL) after 24 h. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-5% EtOAc for 2-10 cv, 5% EtOAc for 10-13 cv, 5-10% EtOAc for 10-20 cv, 10% EtOAc for 20-27 cv and ramped to 100% EtOAc for 27-30 cv and then held at 100% EtOAc for 30-35 cv on a 12 g silica column to afford **3.9e** in 66% yield (21 mg, 0.07 mmol) as a light brown solid. ^{19}F NMR (376 MHz, C_6D6) δ -93.0 – -93.2 (m, 2F), -141.9 – -142.1 (m, 2F). ^{1}H NMR (400 MHz, C_6D6) δ 3.64 (s, 3H), 3.50 (s, 3H), 2.56 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 143.5 (dddd, *J* = 243.3, 17.3, 13.5, 2.4 Hz), 141.4 – 138.4 (m), 137.2, 130.9 – 130.3 (m), 129.1, 110.3, 105.1, 50.9, 31.0, 11.9, 11.1. FT-IR cm^{-1} 1699, 1107. GC/MS (*m/z*, relative intensity) 316 (M+, 100), 301 (90), 285 (80), 256 (32), 56 (98). mp 136-138 °C.

Synthesis of 3.9f (methyl 1,2,5-trimethyl-4-(2,3,5,6-tetrafluoro-4(methoxycarbonyl)phenyl)-1H-pyrrole-3-carboxylate)



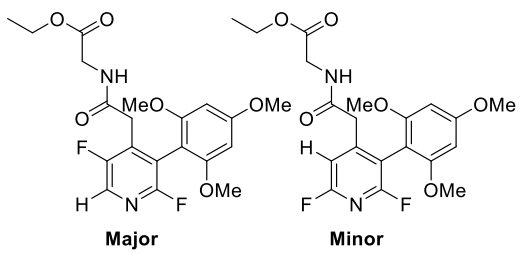
The **General procedure B** was followed using methyl 2,3,4,5,6-pentafluorobenzoate (88.6 µL, 0.6 mmol, 3 equiv), methyl 1,2,5-trimethyl-1H-pyrrole-3-carboxylate (33.4 mg, 0.2 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (41.7 µL, 0.24 mmol, 1.2 equiv), $KHCO_3$ (24 mg, 0.24 mmol, 1.2 equiv) and 2.0 mL of stock solution of $Ir(ppy)_3$ (0.32 mg, 0.0005 mmol, 0.0025 equiv) in CH_3CN was used. This reaction was carried out at 45 °C. Two consecutive additions of 01.2 equiv of *N*,*N*-diisopropylethylamine (41.7 µL) were done after 20 h intervals. After complete consumption of fluorinated starting material another 3 equiv of methyl 2,3,4,5,6-pentafluorobenzoate (88.6 µL), 0.0025 equiv of $Ir(ppy)_3$ (0.32 mg), 1.2 equiv of *N*,*N*-diisopropylethylamine (41.7 µL) was added and degassed. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-5% EtOAc for 2-10 cv, 5% EtOAc for 10-12 cv, 5-20% EtOAc for 12-25 cv, 20% EtOAc for 25-30 cv, 20-45% EtOAc for 30-32 cv, 45% EtOAc for 32-35 cv and ramped to 100% EtOAc for 35-37 cv and then held at 100% EtOAc for 37-40 cv on a 24 g silica column to afford **3.9f** in 66% yield (21 mg, 0.07 mmol) as an off-white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -139.4 – -139.6 (m, 2F), -141.4 – -141.6 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 3.62 (s, 3H), 3.49 (s, 3H), 2.56 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 160.7, 146.0 – 142.9 (m), 146.0 – 142.9 (m), 136.7, 128.7, 120.2 (t, *J* = 18.5 Hz), 110.4, 110.3 – 109.9 (m), 105.3 (t, *J* = 2.5 Hz), 53.1, 50.7, 30.8, 11.8, 10.9. FT-IR cm^{-1} 1735, 1691, 1109. GC/MS (*m/z*, relative intensity) 373 (M+, 98), 358 (70), 342 (68), 56 (100). mp 122-123 °C.

Synthesis of 3.10c (methyl 4,6-difluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)



The **General procedure C** was followed using methyl 3,4,6-trifluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate (**3.10b**) (21.4 mg, 0.05 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (10.4 µL, 0.06 mmol, 1.2 equiv) and 0.5 mL of stock solution of $Ir(ppy)_3$ (0.08 mg, 0.000125 mmol, 0.0025 equiv) in CH_3CN was used. Four consecutive additions of 1.2 equiv of *N*,*N*-diisopropylethylamine (10.4 µL) were done after 20 h intervals. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-20% EtOAc for 2-10 cv, 20% EtOAc for 10-13 cv, 20-40% EtOAc for 13-20 cv, 40% EtOAc for 20-25 cv and ramped to 100% EtOAc for 25-32 cv and then held at 100% EtOAc for 32-35 cv on a 12 g silica column to afford **3.10c** in 83% yield as a mixture of the two isomers shown above (17 mg, 0.04 mmol, rr= 6.3:1) as a light yellow solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2 (d, *J* = 7.0 Hz, 1F, major), -115.9 (t, *J* = 8.4 Hz, 1F, major), -119.6 (dd, *J* = 16.6, 9.6 Hz, 1F, minor), -120.7 (dd, *J* = 16.8, 5.6 Hz, 1F, minor). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.5 Hz, 1H), 7.06 (dd, *J* = 8.9, 5.8 Hz, 1H, minor), 6.20 (s, 2H), 6.18 (s, 2H, minor), 3.85 (s, 3H), 3.76 (s, 2H), 3.71 (s, 3H), 3.69 (s, 6H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 166.1 (t, *J* = 3.2 Hz), 161.5, 160.7 (dd, *J* = 74.1, 7.9 Hz), 158.3, 158.2 (dd, *J* = 73.6, 8.1 Hz), 158.2, 132.8 (dd, *J* = 9.5, 4.9 Hz), 118.1 (dd, *J* = 204.7, 21.6 Hz), 113.9 (t, *J* = 21.4 Hz), 112.3 (dd, *J* = 24.1, 3.6 Hz), 103.6, 90.7, 55.8, 55.3, 52.3, 52.1, 28.7 – 28.1 (br s). FT-IR cm^{-1} 1730, 1608, 1583, 1120. GC/MS (*m/z*, relative intensity) 410 (M+, 100), 257 (40), 59 (78). mp 124-125 °C.

Synthesis of 3.10f (ethyl (2-(2,5-difluoro-3-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)

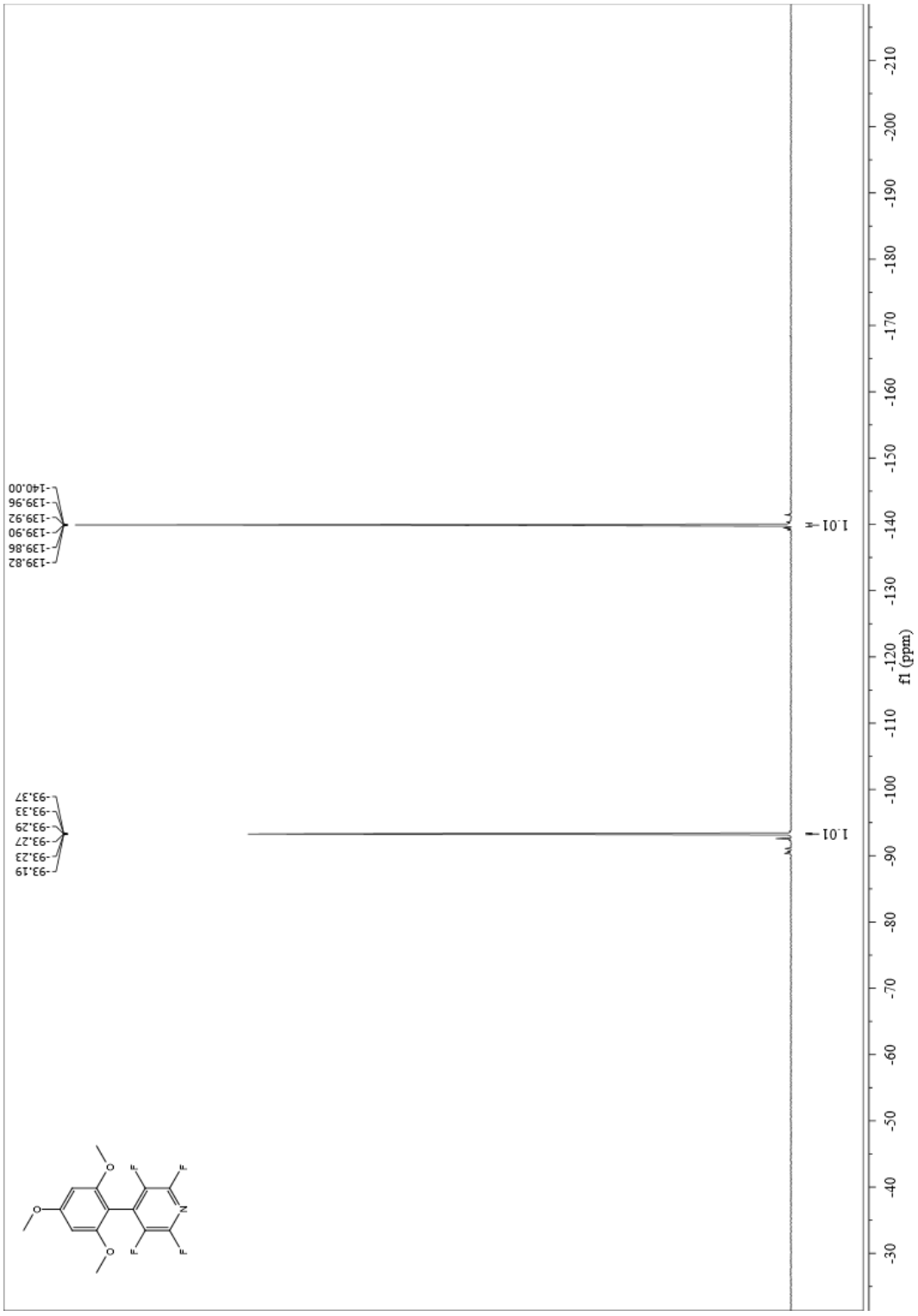


The **General procedure C** was followed using ethyl (2-(2,3,6-trifluoro-5-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate (**3.10e**) (22.9 mg, 0.05 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (10.4 µL, 0.06 mmol, 1.2 equiv) and 0.5 mL of stock solution of $Ir(ppy)_3$ (0.08 mg, 0.000125 mmol, 0.0025 equiv) in CH_3CN was used. Three consecutive additions of 2.4 equiv of *N*,*N*-diisopropylethylamine (20.8 µL) were done after 20 h intervals. After 48 h another 0.0025 equiv of $Ir(ppy)_3$ (0.08 mg) and 2.4 equiv of *N*,*N*-diisopropylethylamine (20.8 µL) was added and degassed. The crude material was purified by flash chromatography using hexane: ethyl acetate (0% EtOAc for 2 cv, 0-10% EtOAc for 2-10 cv, 10-70% EtOAc for 10-20 cv, 70% EtOAc for 20-25 cv and ramped to 100% EtOAc for 25-27 cv and then held at 100% EtOAc for 27-29 cv on a 24 g silica column to afford **3.10f** in 81% yield (18 mg, 0.04 mmol, rr= 2:1) as a light yellow solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.5 (d, *J* = 11.5 Hz, P2), -71.5 (d, *J* = 11.5 Hz, P2), -71.9 (d, *J* = 27.7 Hz, P1), -134.1 (d, *J* = 27.7 Hz, P1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.94 (s, 1H, minor), 6.21 (s, 2H), 6.20 (s, 2H, minor), 5.98 (s, 1H), 5.97 (s, 1H, minor), 4.17 (p, *J* = 6.7 Hz, 2H, major and minor), 3.90 (t, *J* = 4.9 Hz, 2H, major and minor), 3.86 (s, 3H, major and minor), 3.70 (s, 6H, major and minor), 3.70 (s, 6H, major and minor), 3.49 (s, 2H), 3.44 (s, 2H, minor), 1.25 (td, *J* = 7.4, 4.1 Hz, 3H, major and minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5 , 168.9 (minor), 168.0 , 162.8 (minor), 162.7 , 158.7 , 158.6 , 157.7 (d, *J* = 235.1 Hz), 156.5 (dd, *J* = 251.3, 4.1 Hz), 153.7 (dd, *J* = 8.4, 4.0 Hz, minor), 136.7 (dd, *J* = 15.4, 4.9 Hz), 132.6 (dd, *J* = 28.2, 16.5 Hz), 119.0 (d, *J* = 36.9 Hz), 113.7 (dd, *J* = 30.1, 5.8 Hz, minor), 106.5 (dd, *J* = 34.9, 5.4 Hz, minor), 100.7 (dd, *J* = 10.0, 2.5 Hz), 91.0 (minor), 61.7 (minor) ,61.6,

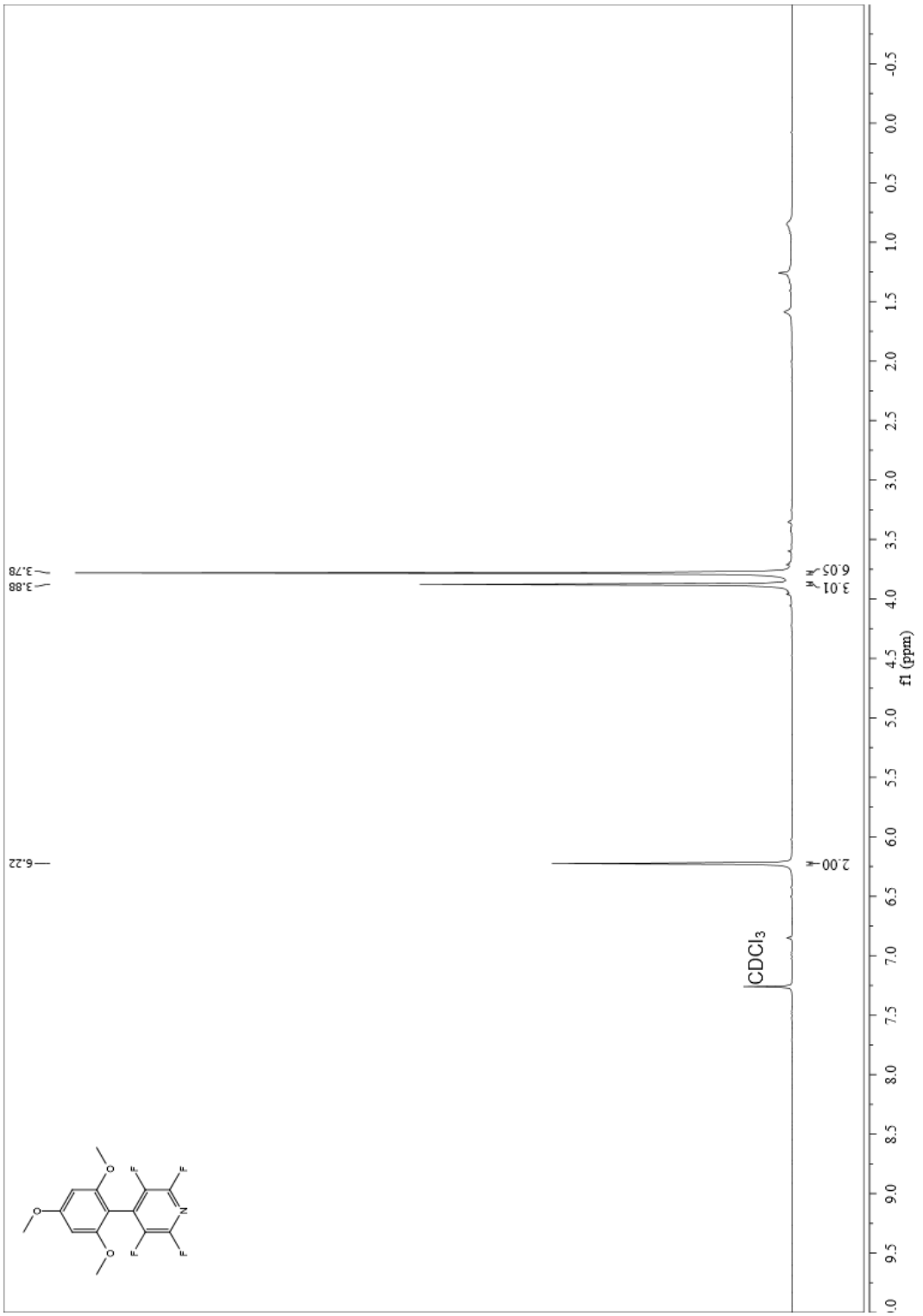
56.0 (minor), 55.9 (minor), 55.6, 41.7, 40.6 (minor), 35.0, 14.2. FT-IR cm^{-1} 3275, 1747, 1606. GC/MS (*m/z*, relative intensity) 424 (M+, 45), 322 (55), 263 (100), 220 (80). mp 172-175 ^{o}C.

NMR, GC and MS spectra for Chapter III

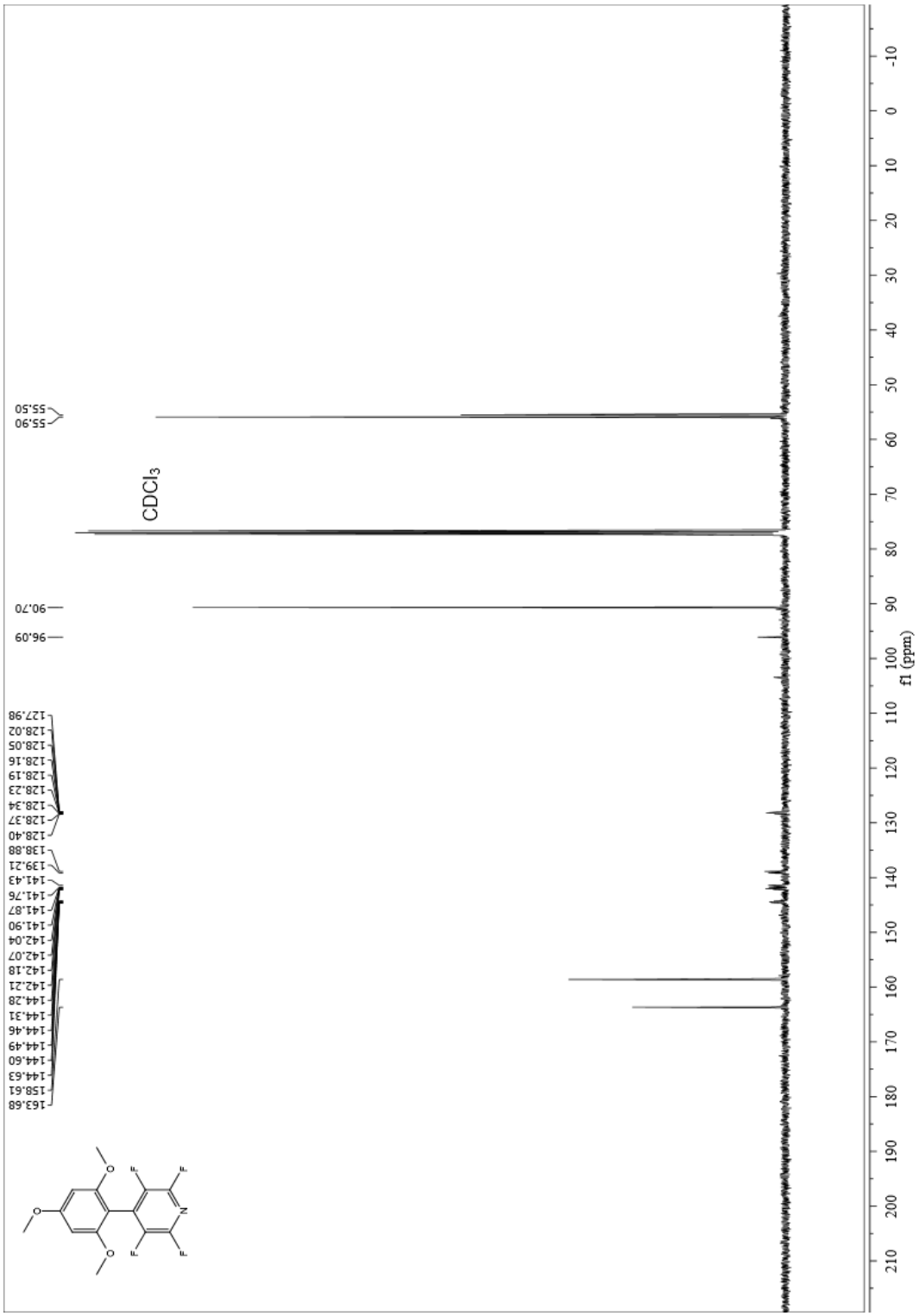
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6a (2,3,5,6-tetrafluoro-4-(2,4,6-trimethoxyphenyl)pyridine)



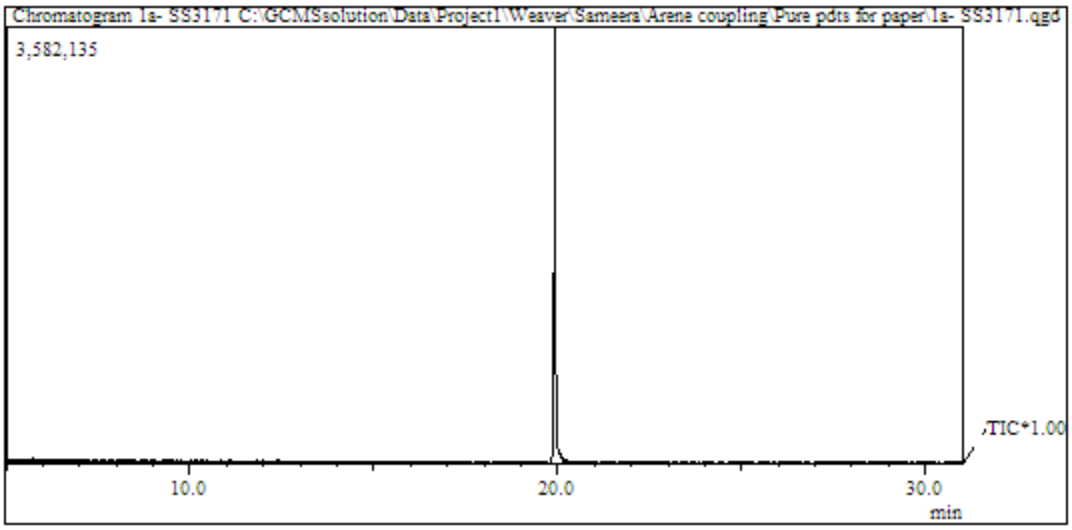
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6a (2,3,5,6-tetrafluoro-4-(2,4,6-trimethoxyphenyl)pyridine)

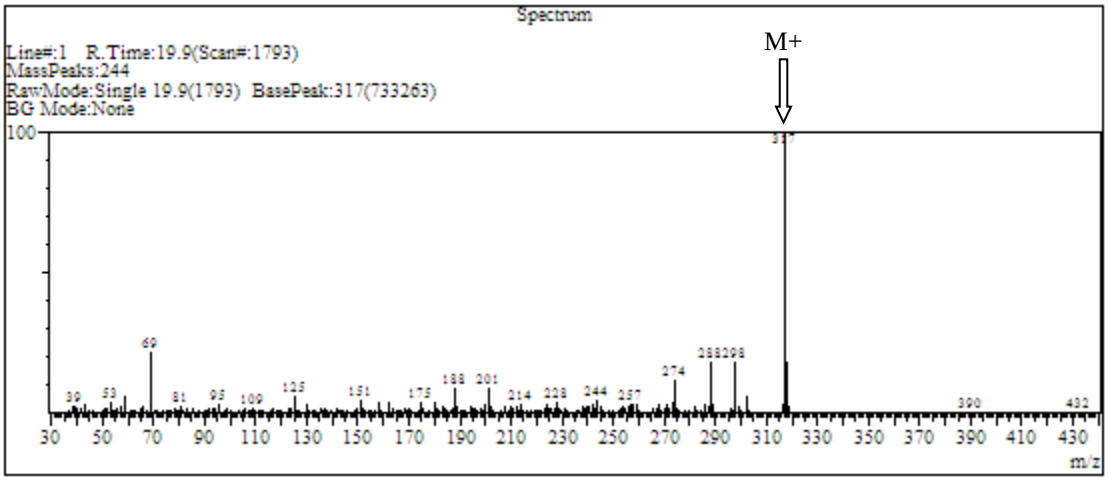


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6a (2,3,5,6-tetrafluoro-4-(2,4,6-trimethoxyphenyl)pyridine)

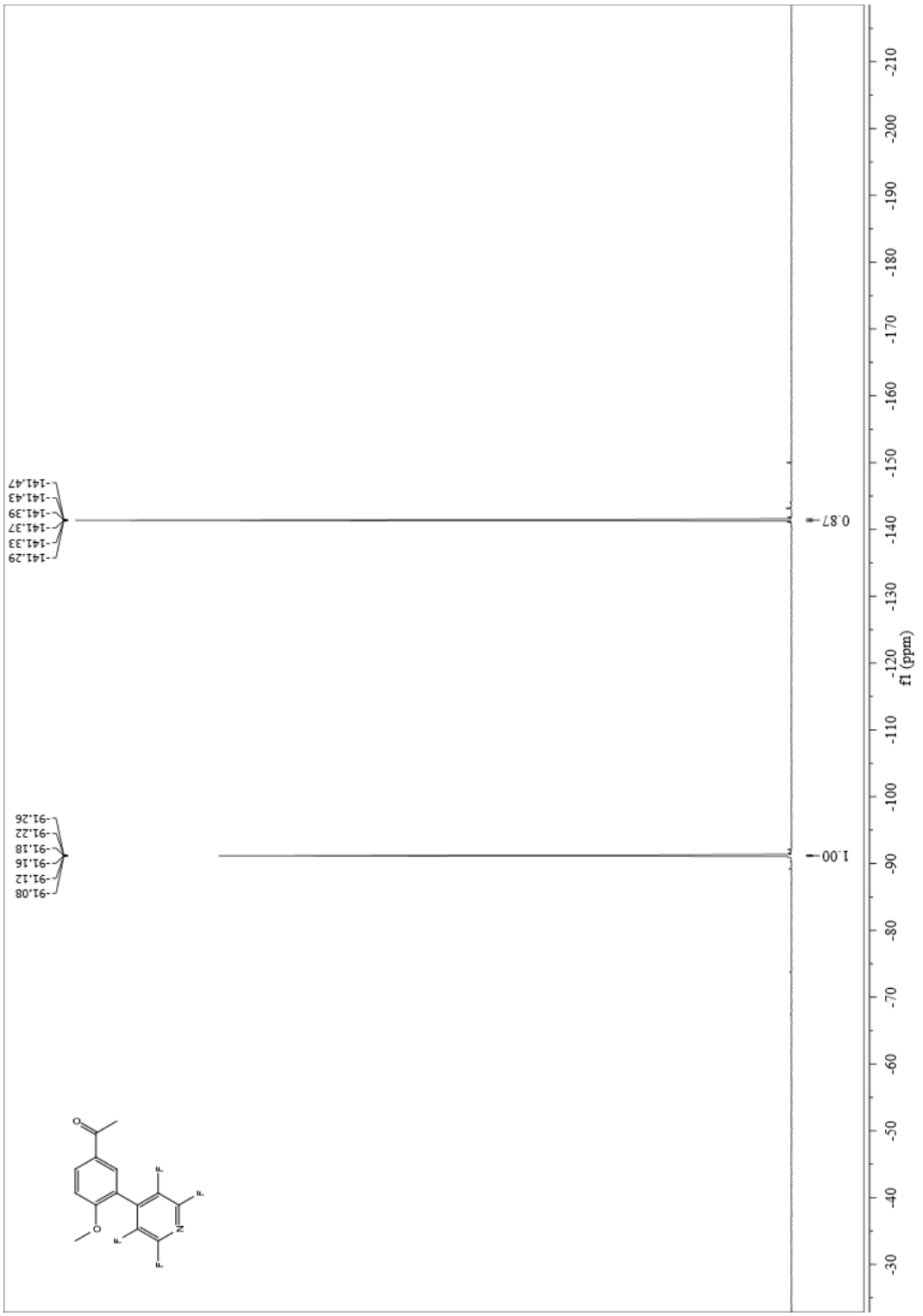


GC and MS of 3.6a (2,3,5,6-tetrafluoro-4-(2,4,6-trimethoxyphenyl)pyridine)

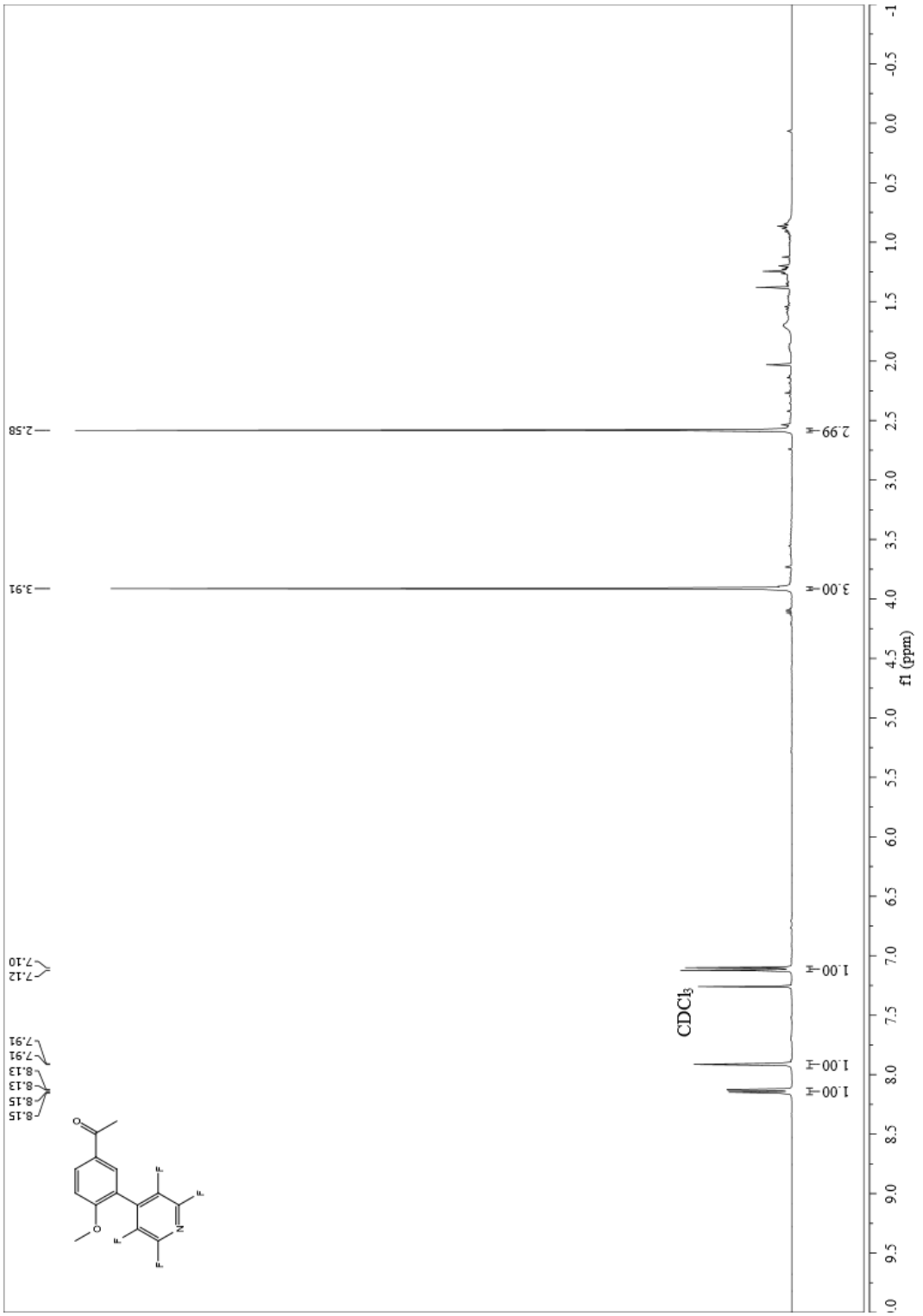




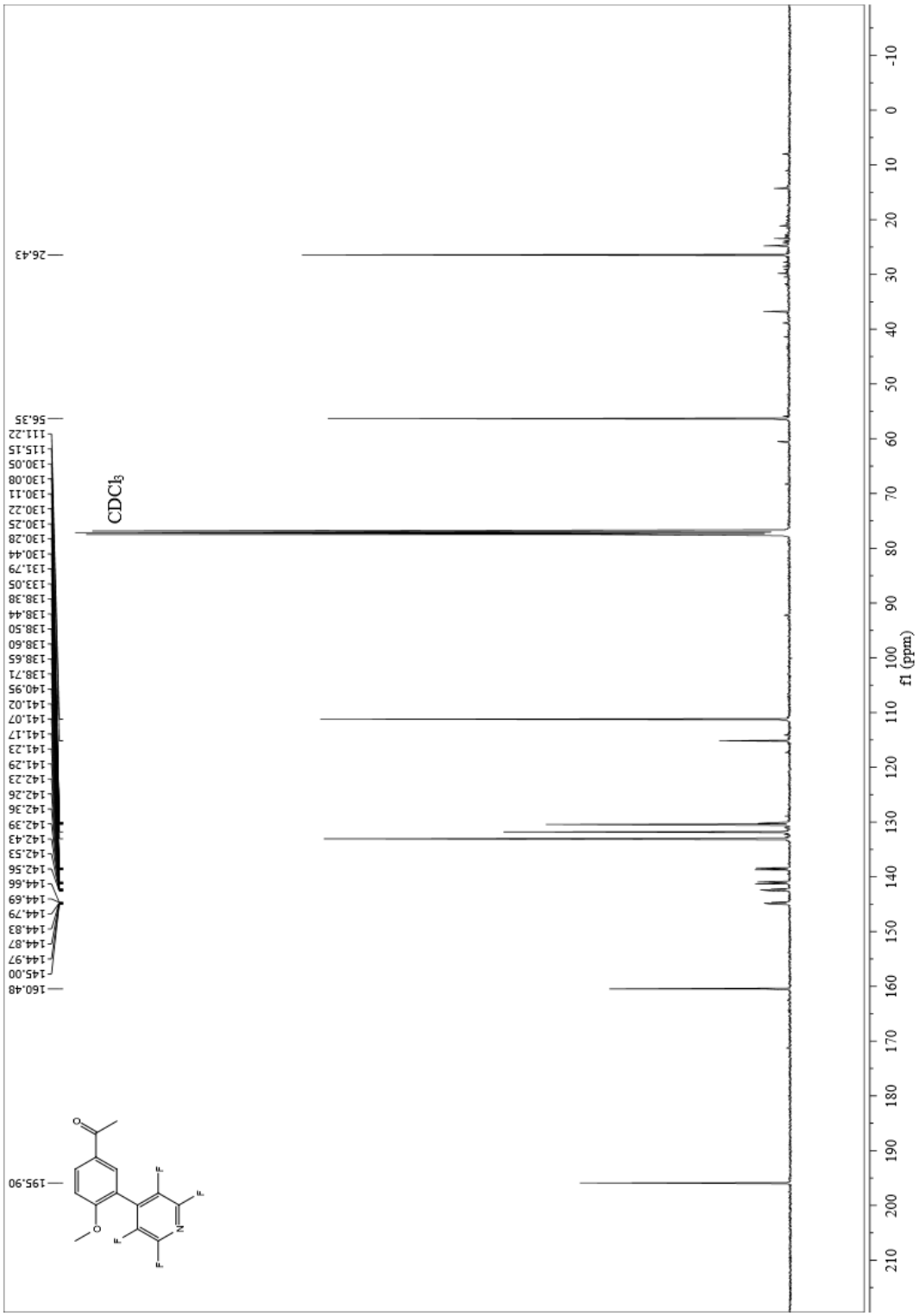
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6b (1-(4-methoxy-3-(perfluoropyridin-4-yl)phenyl)ethan-1-one)



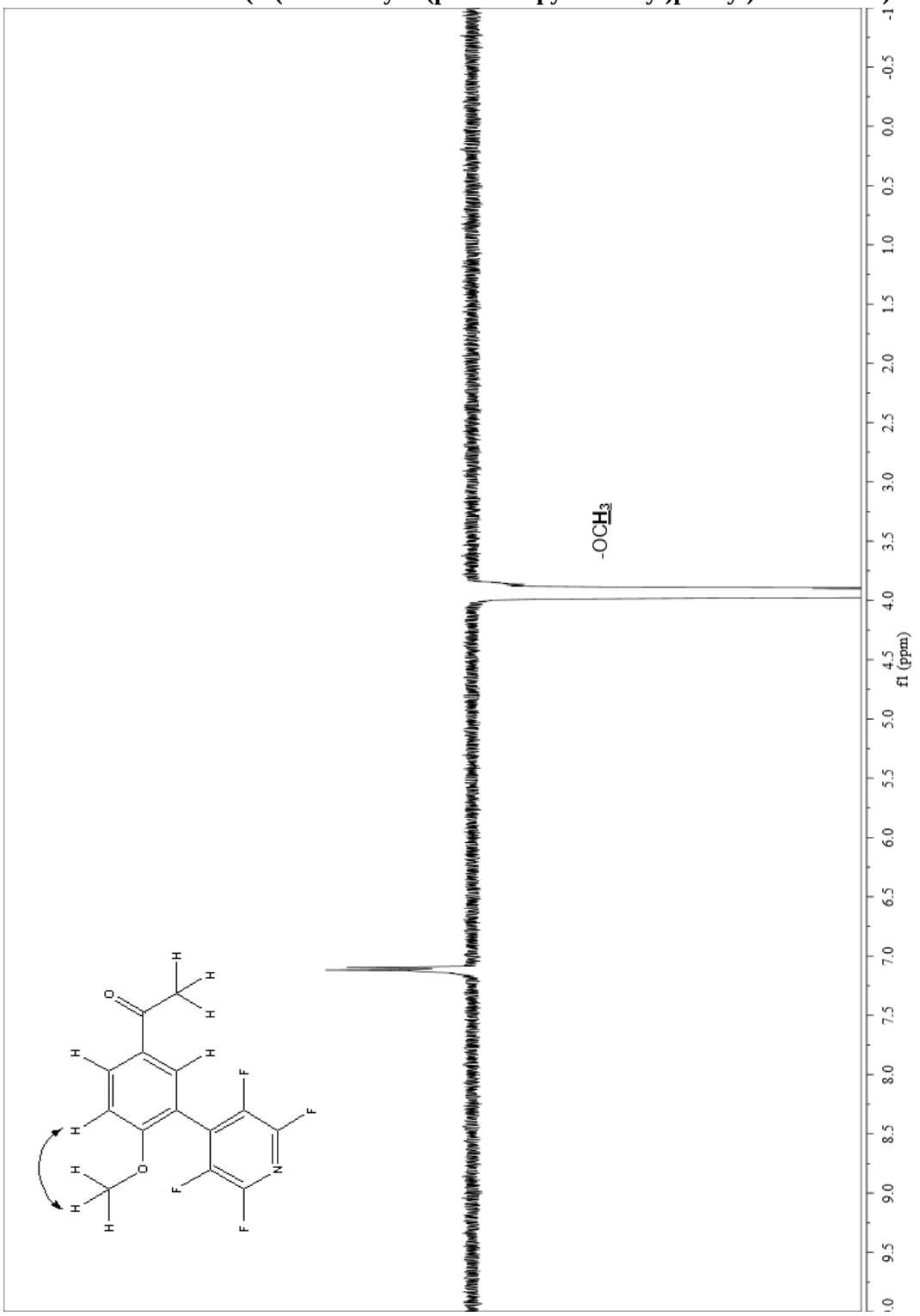
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6b (1-(4-methoxy-3-(perfluoropyridin-4-yl)phenyl)ethan-1-one)



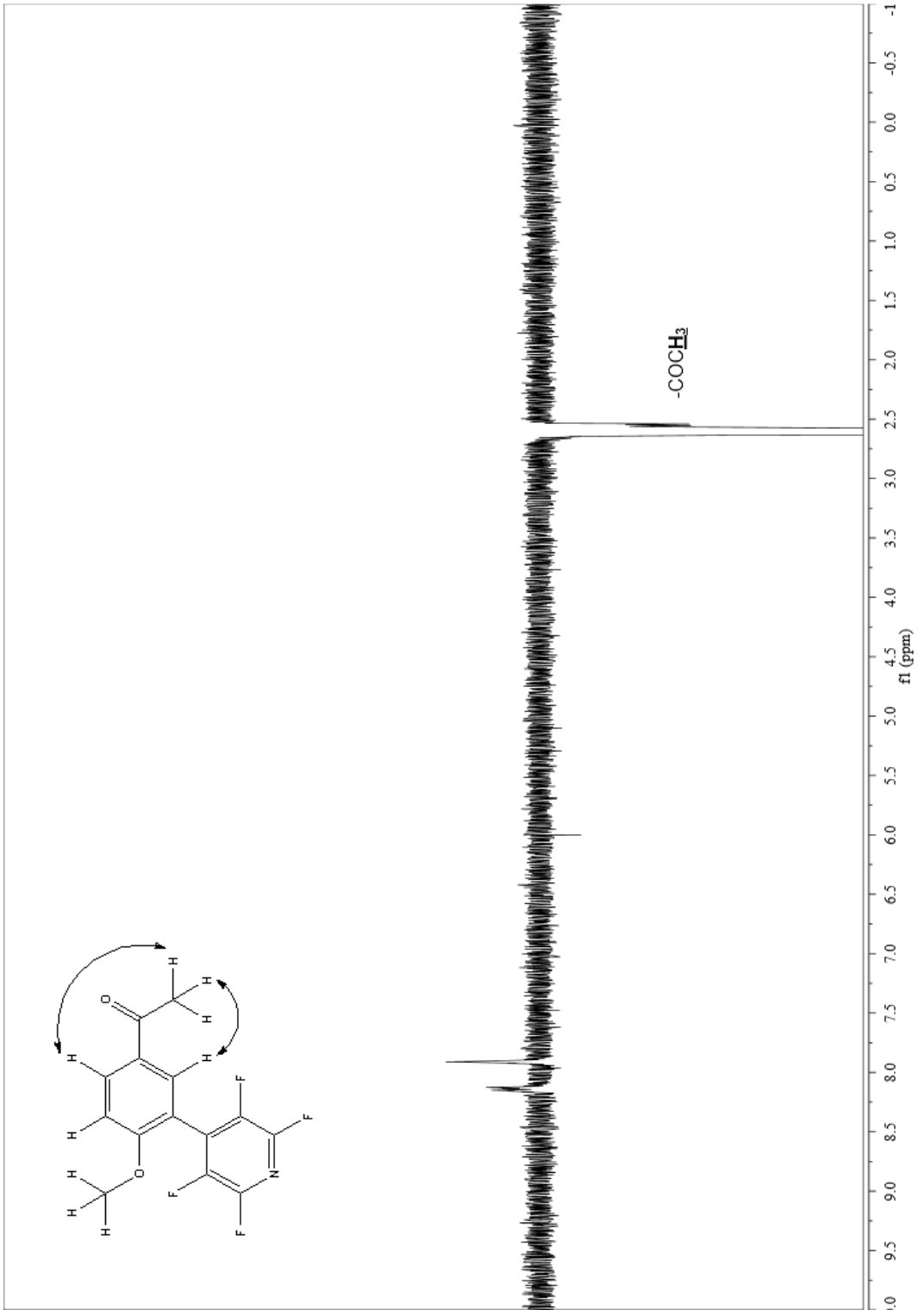
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6b (1-(4-methoxy-3-(perfluoropyridin-4-yl)phenyl)ethan-1-one)



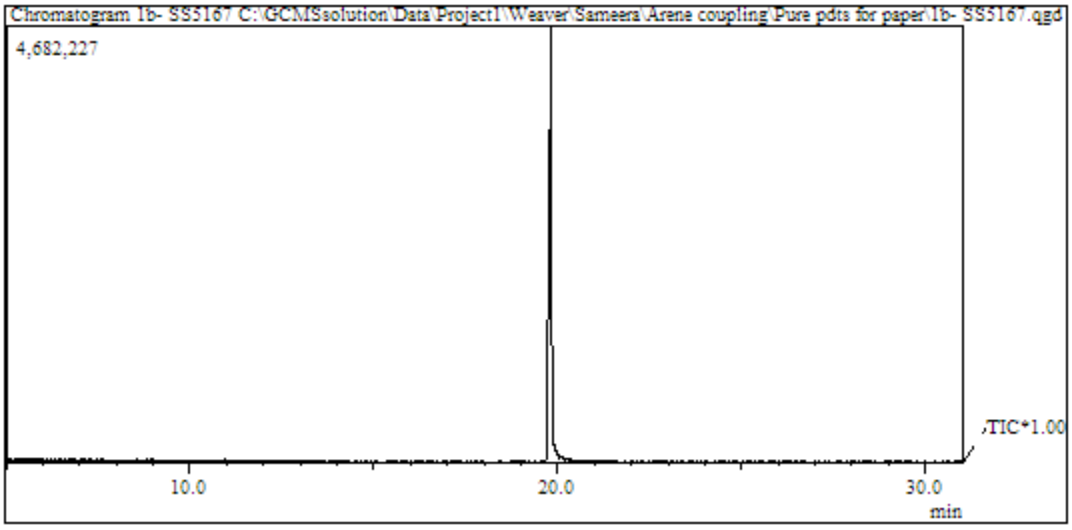
^{1}H-^{1}H NOESY of 3.6b (1-(4-methoxy-3-(perfluoropyridin-4-yl)phenyl)ethan-1-one)

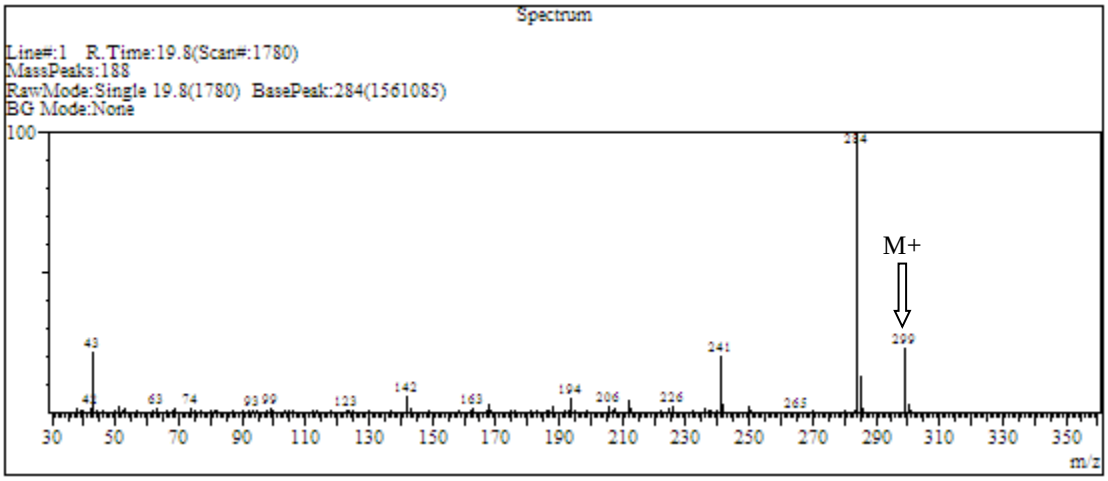


^{1}H-^{1}H NOESY of 3.6b (1-(4-methoxy-3-(perfluoropyridin-4-yl)phenyl)ethan-1-one)

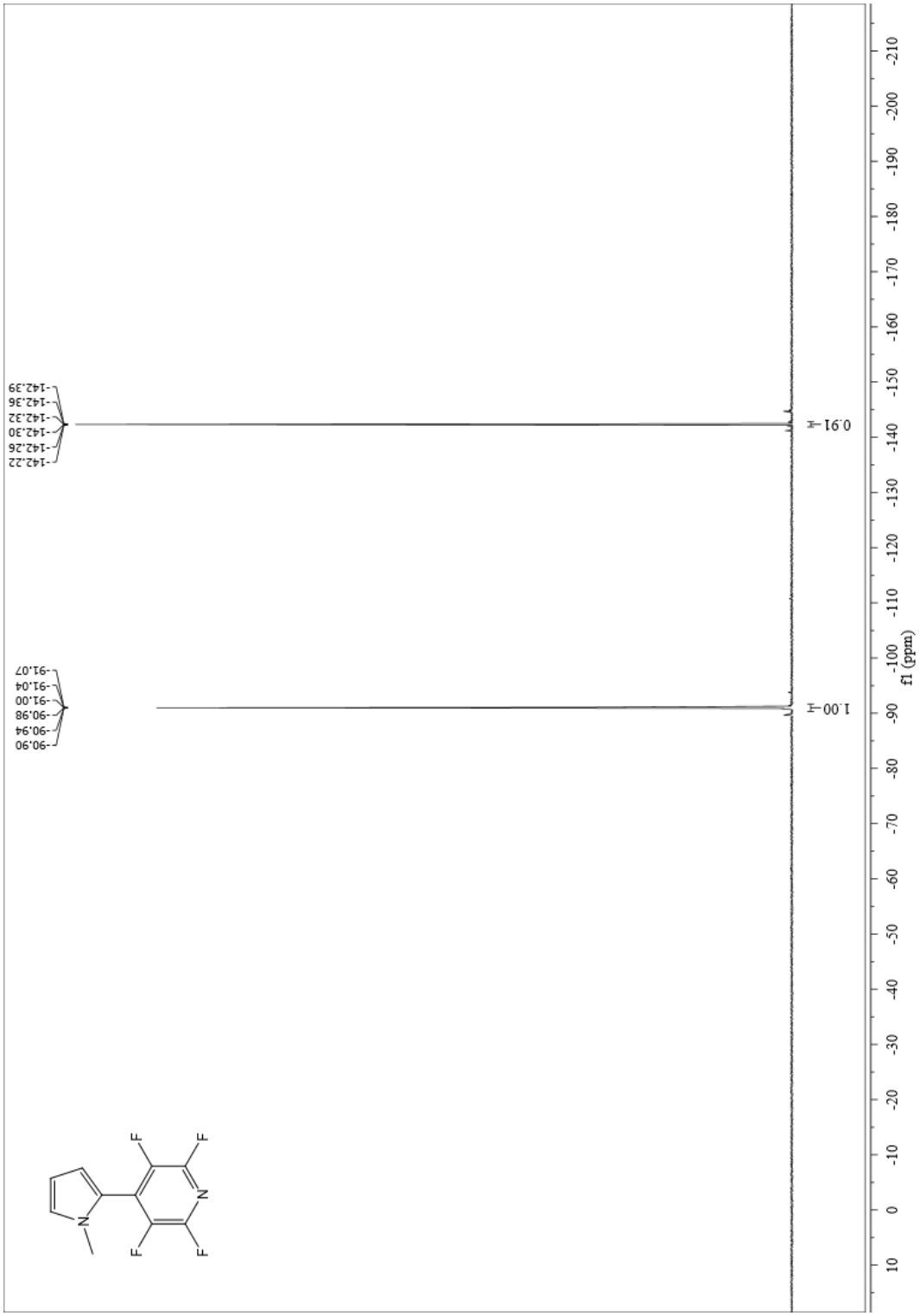


GC and MS of 3.6b (1-(4-methoxy-3-(perfluoropyridin-4-yl)phenyl)ethan-1-one)

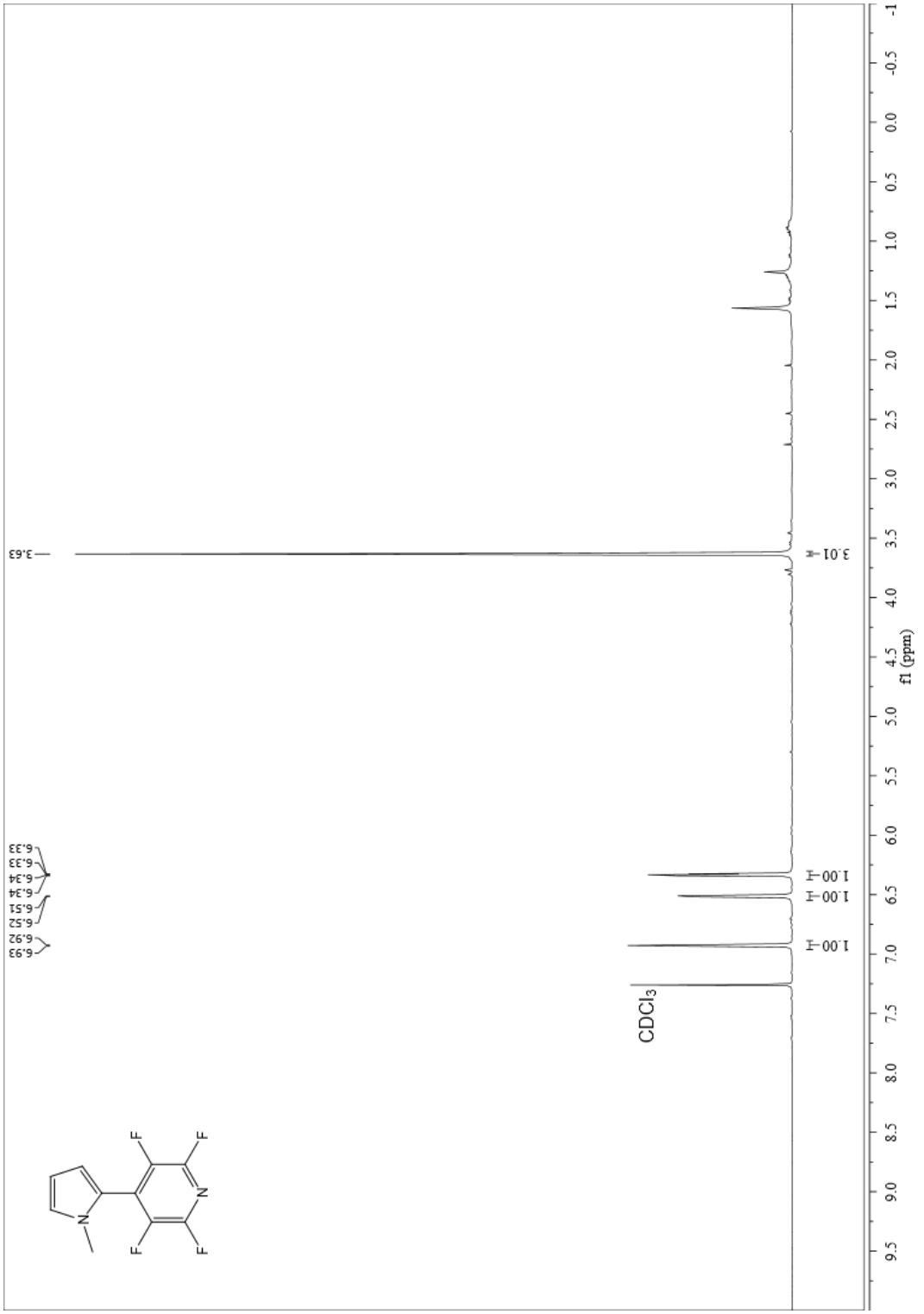




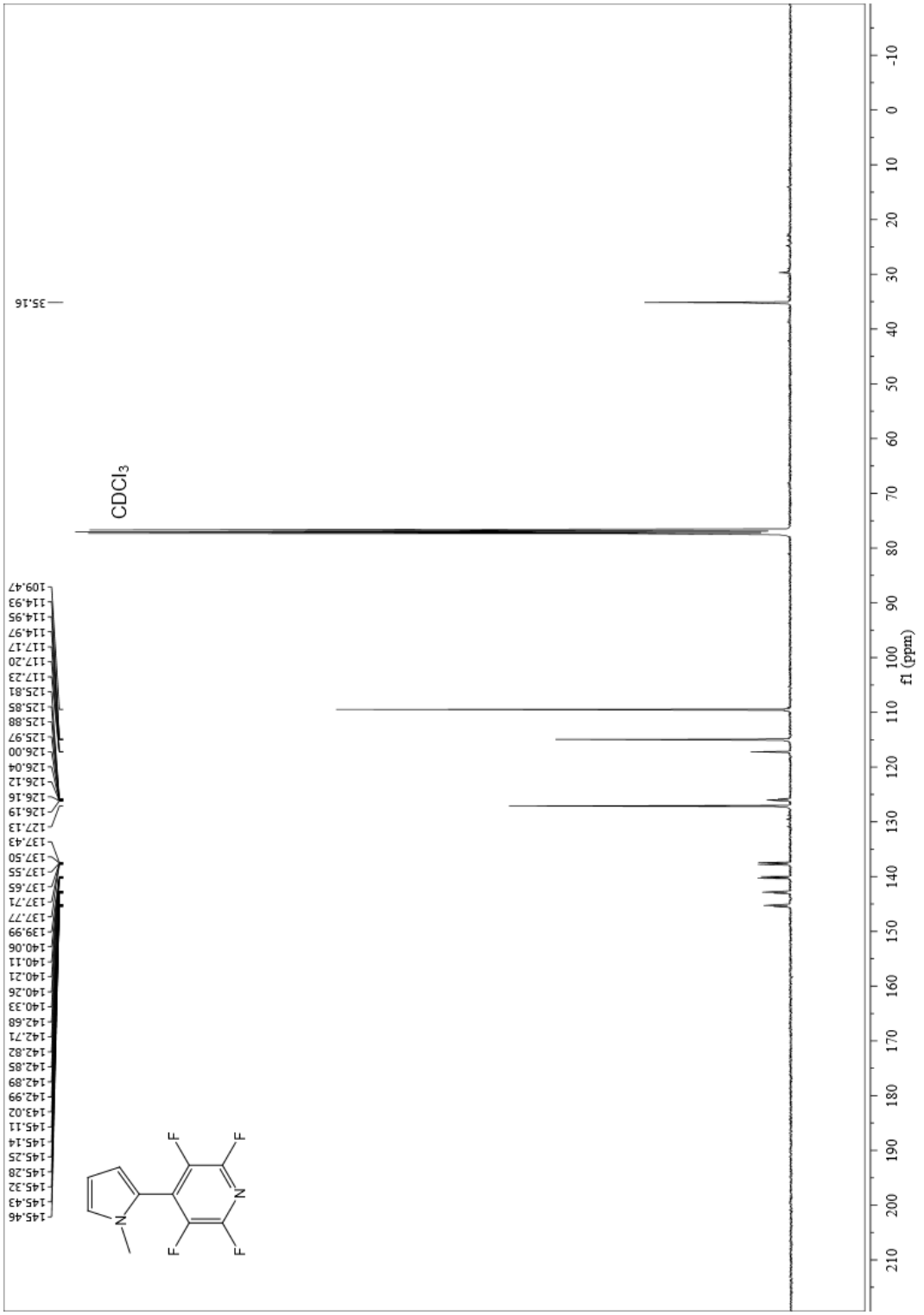
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6c (2,3,5,6-tetrafluoro-4-(1-methyl-1H-pyrrol-2-yl)pyridine)



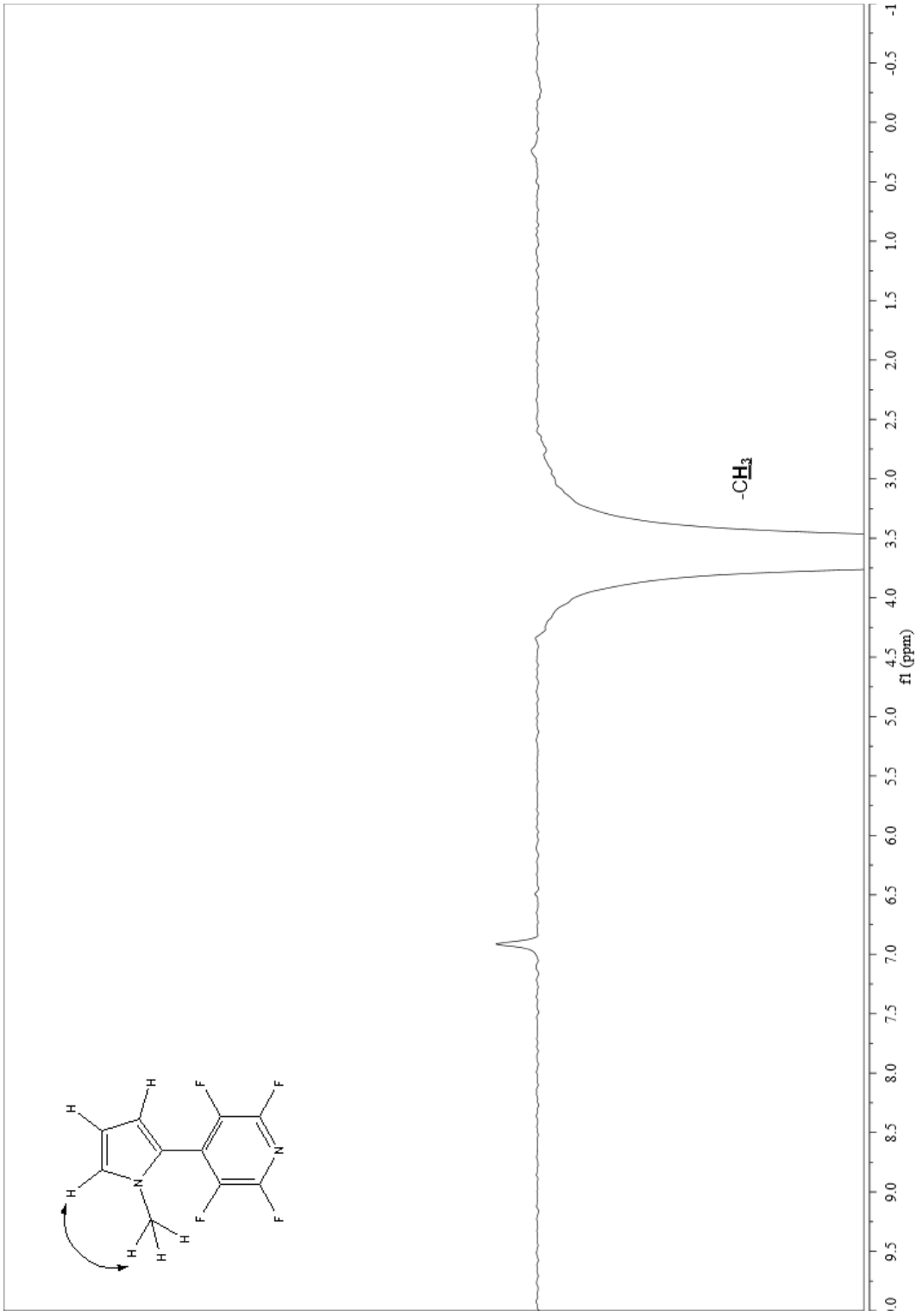
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6c (2,3,5,6-tetrafluoro-4-(1-methyl-1H-pyrrol-2-yl)pyridine)



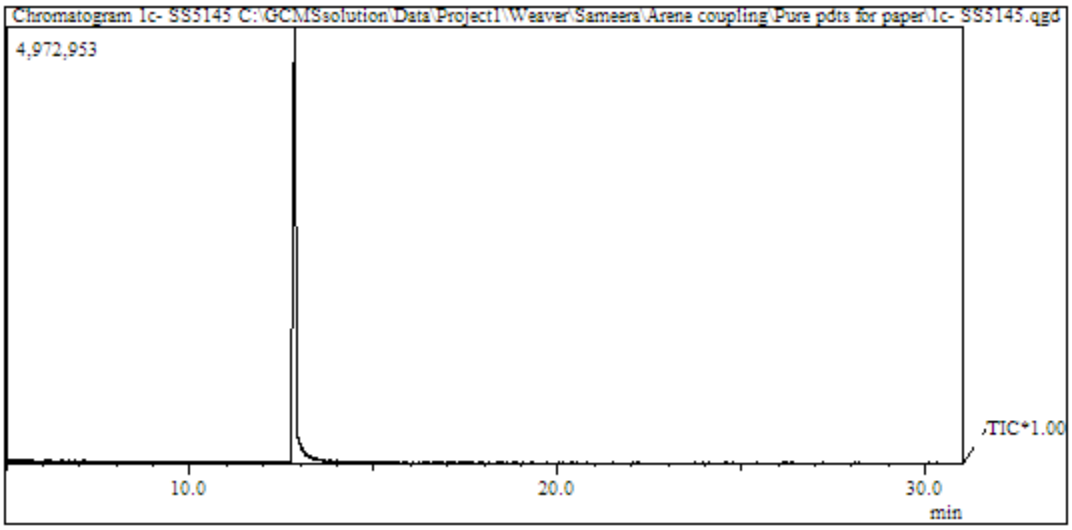
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6c (2,3,5,6-tetrafluoro-4-(1-methyl-1H-pyrrol-2-yl)pyridine)

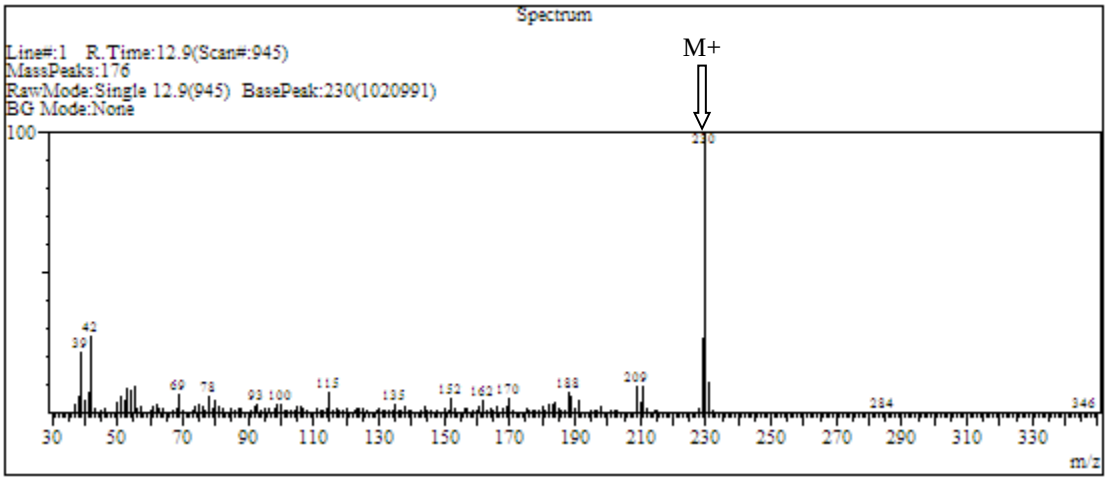


^{1}H-^{1}H NOESY of 3.6c (2,3,5,6-tetrafluoro-4-(1-methyl-1H-pyrrol-2-yl)pyridine))

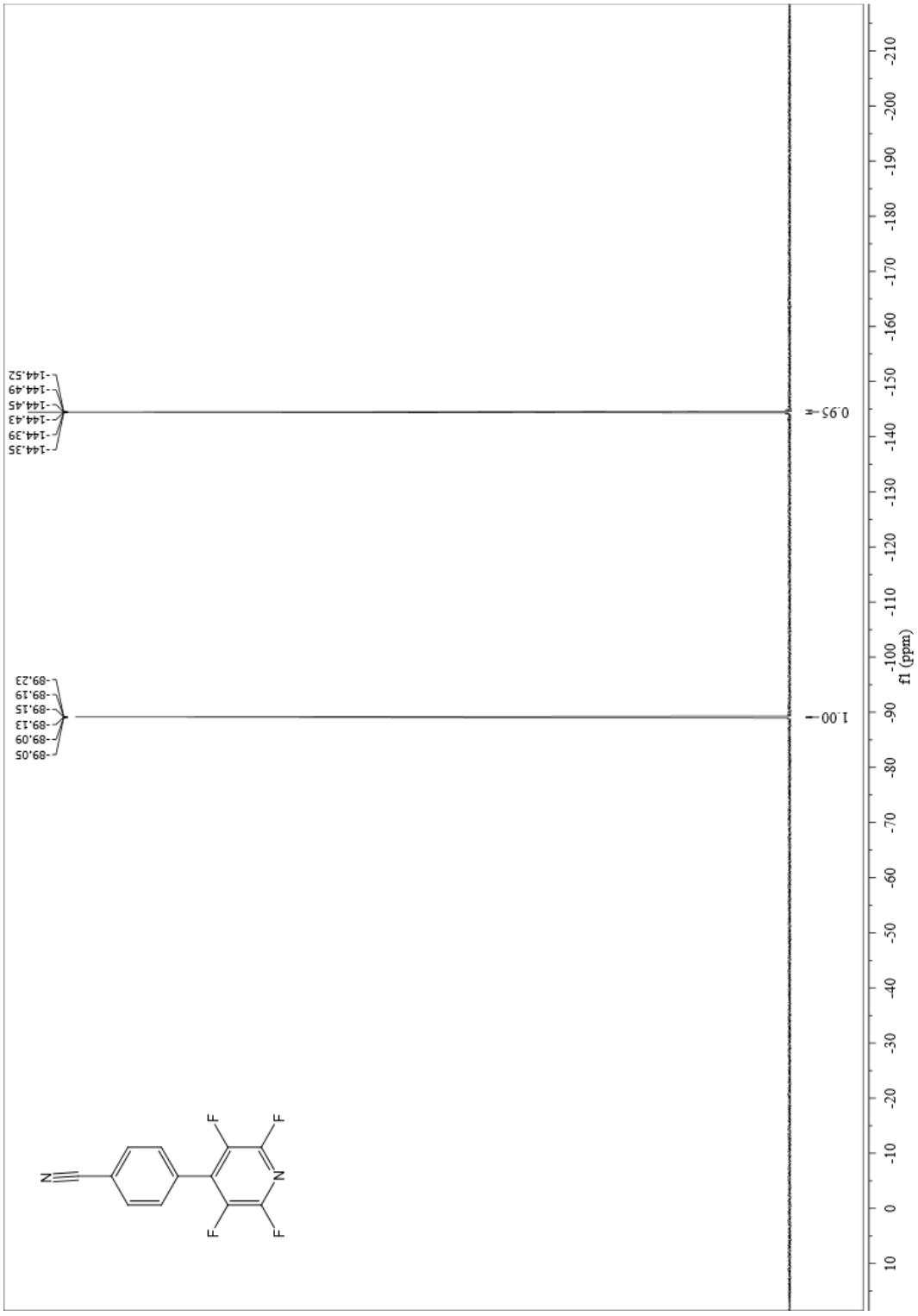


GC and MS of 3.6c (2,3,5,6-tetrafluoro-4-(1-methyl-1H-pyrrol-2-yl)pyridine)

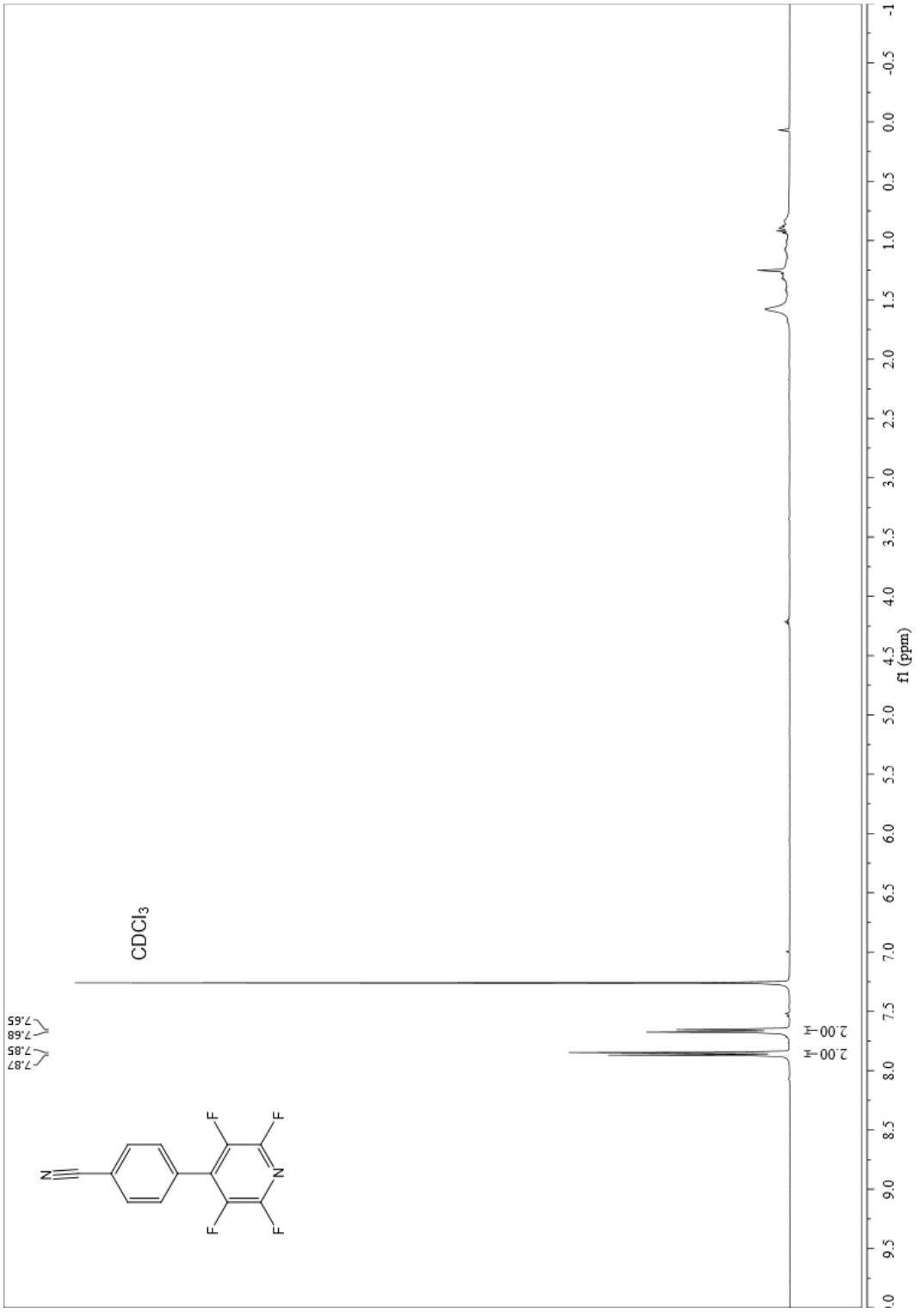




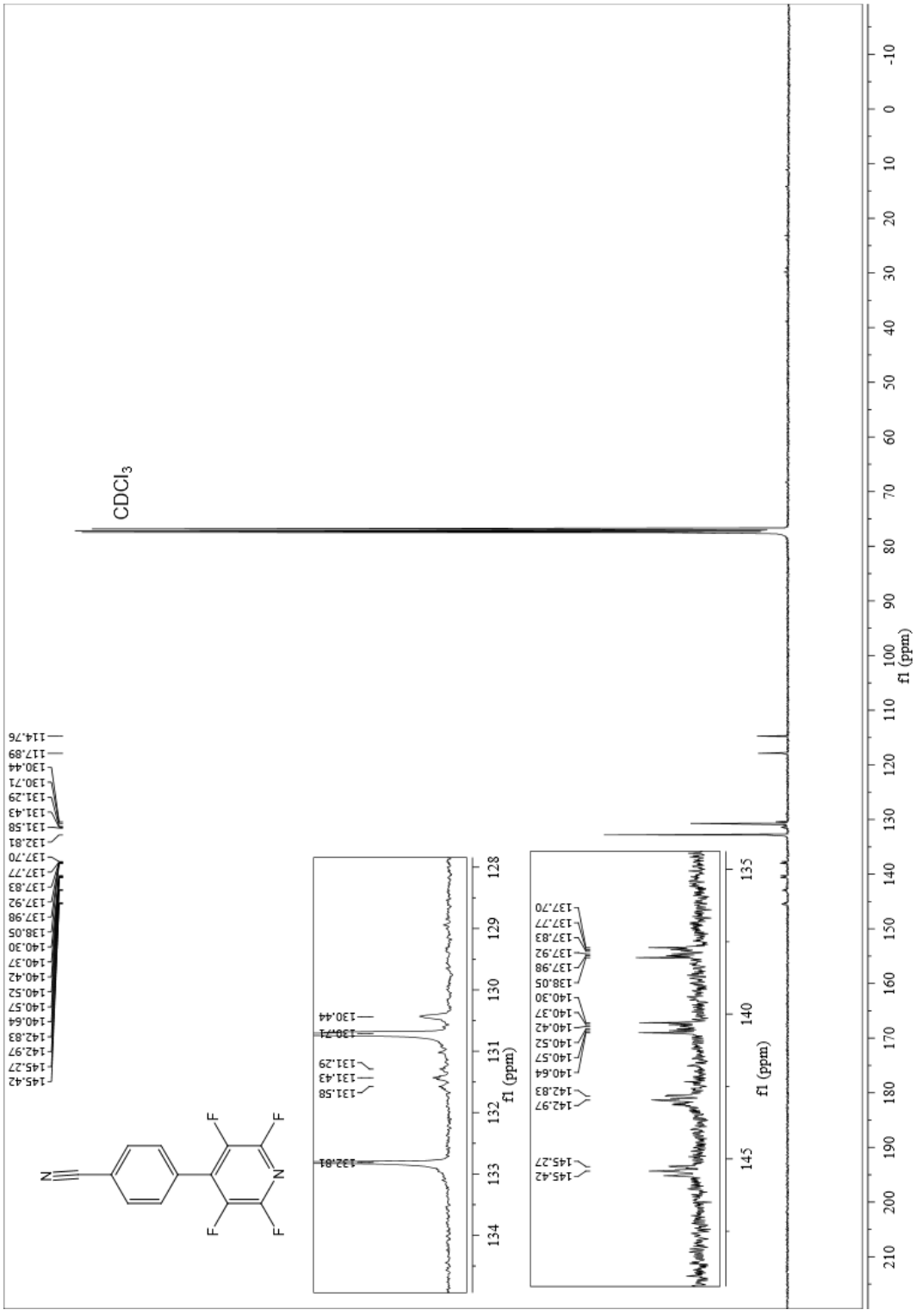
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6d (4-(perfluoropyridin-4-yl)benzonitrile)



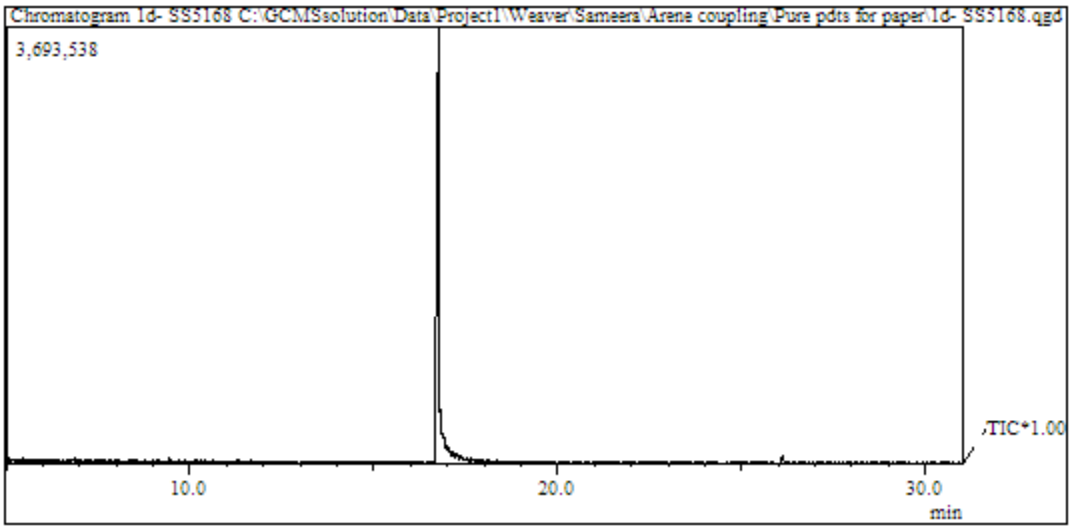
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6d (4-(perfluoropyridin-4-yl)benzonitrile)

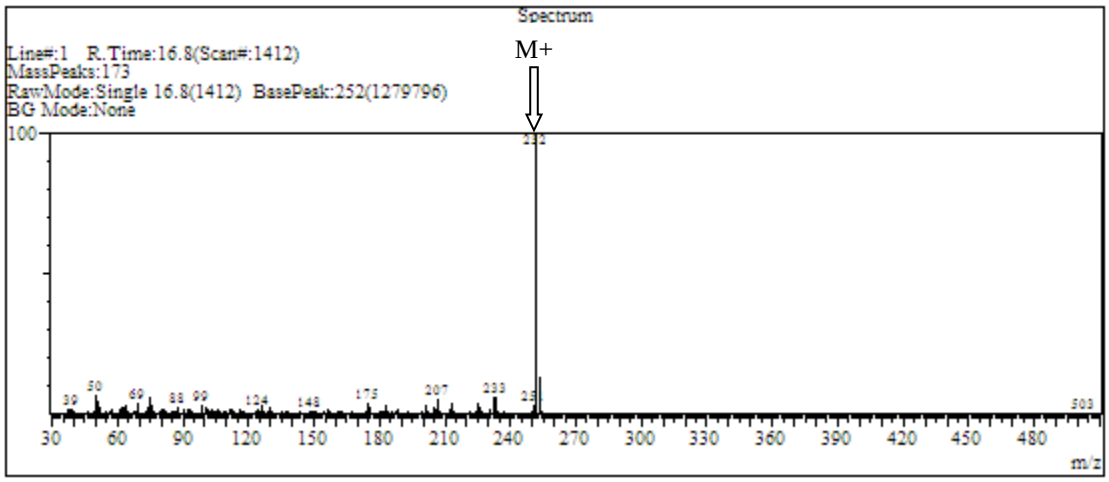


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6d (4-(perfluoropyridin-4-yl)benzonitrile)

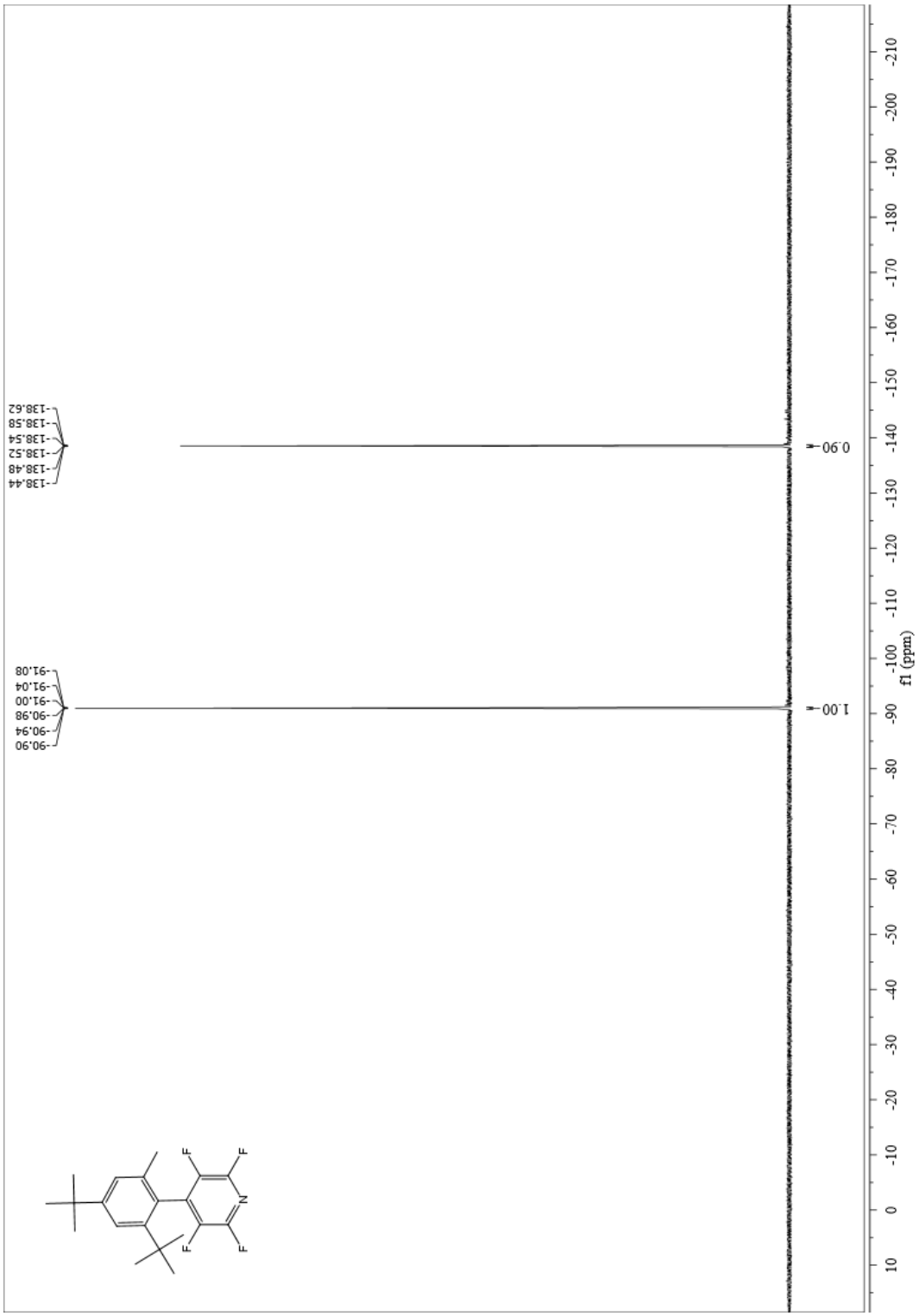


GC and MS of 3.6d (4-(perfluoropyridin-4-yl)benzonitrile)

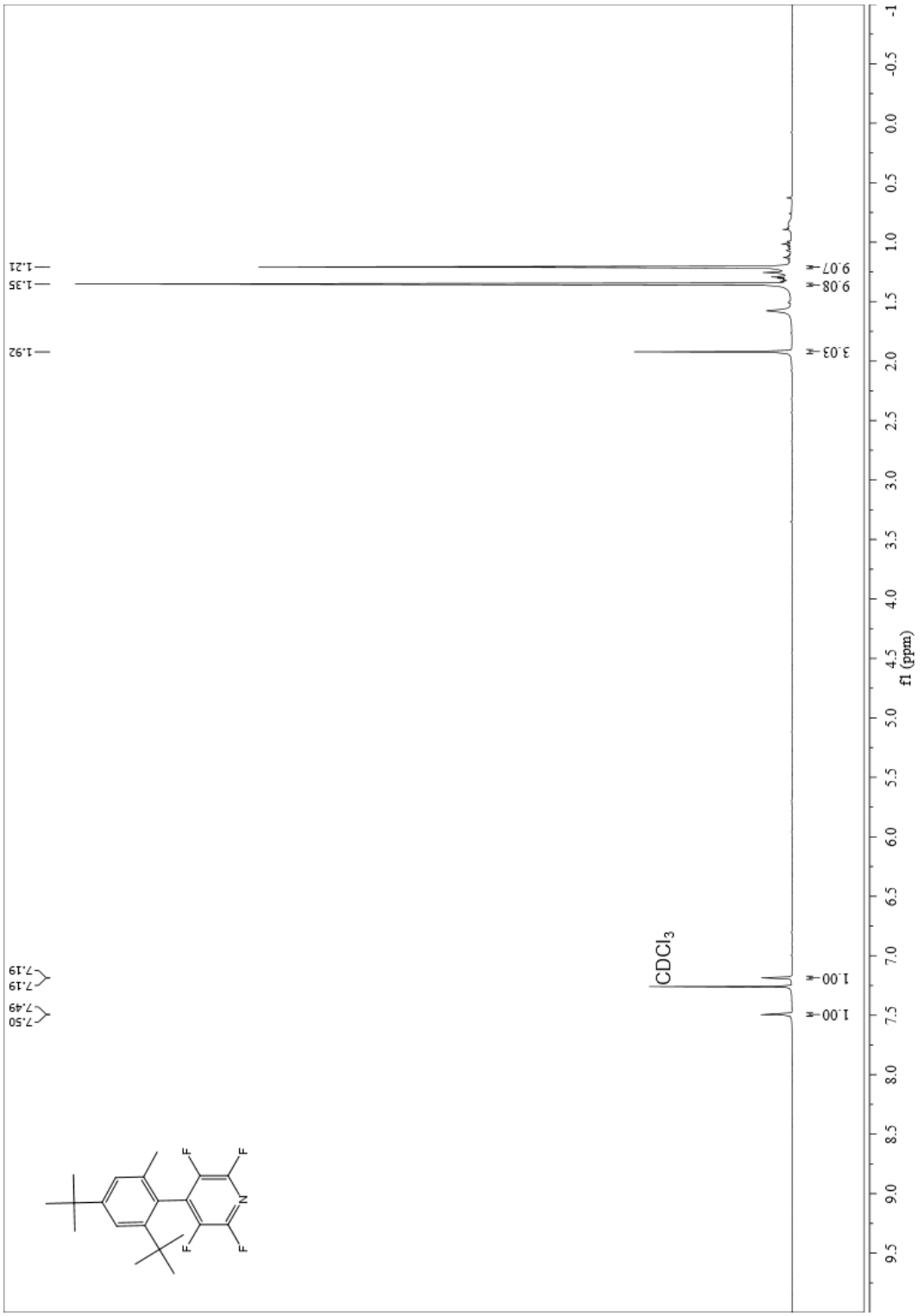




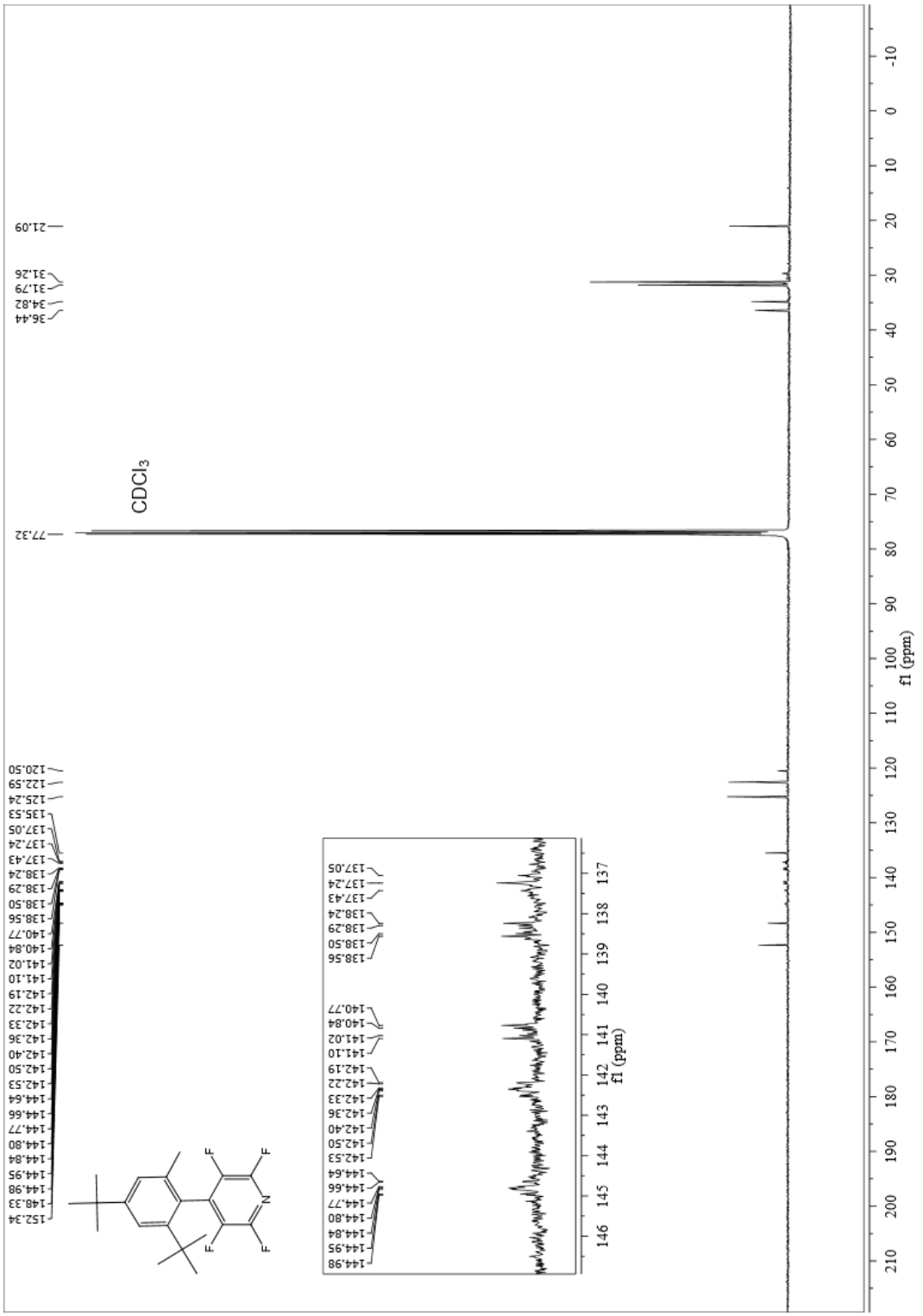
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6e (4-(2,4-di-tert-butyl-6-methylphenyl)-2,3,5,6-tetrafluoropyridine)



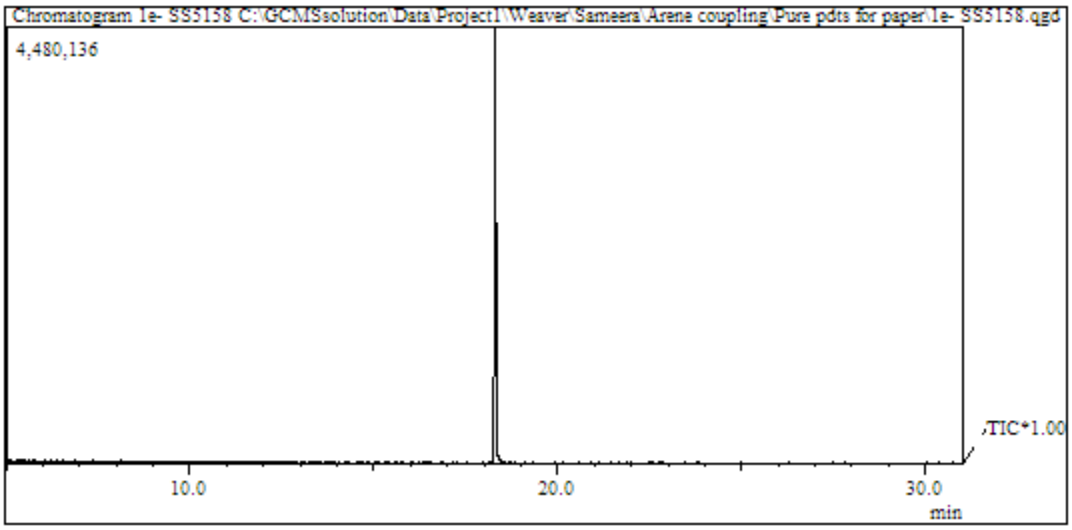
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6e (4-(2,4-di-tert-butyl-6-methylphenyl)-2,3,5,6-tetrafluoropyridine)

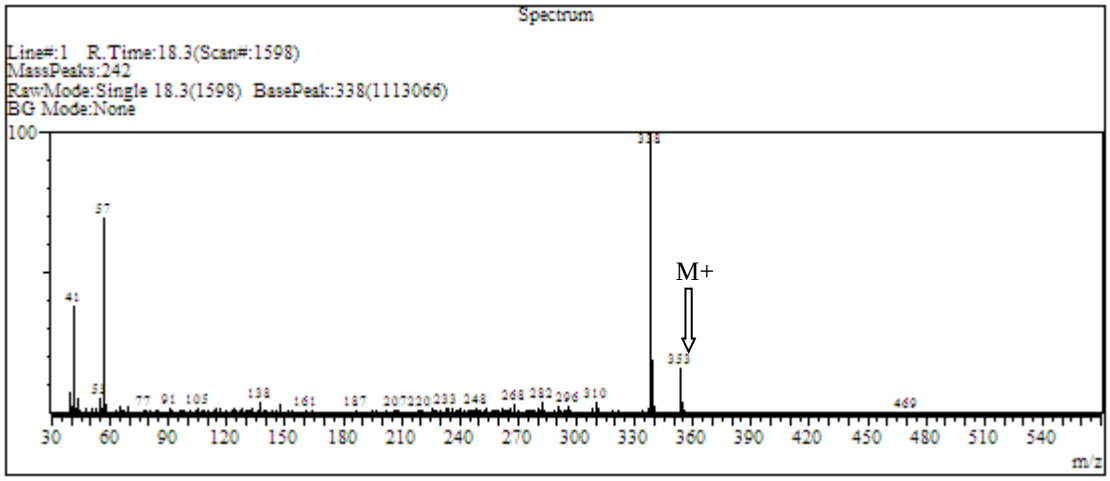


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6e (4-(2,4-di-tert-butyl-6-methylphenyl)-2,3,5,6-tetrafluoropyridine)

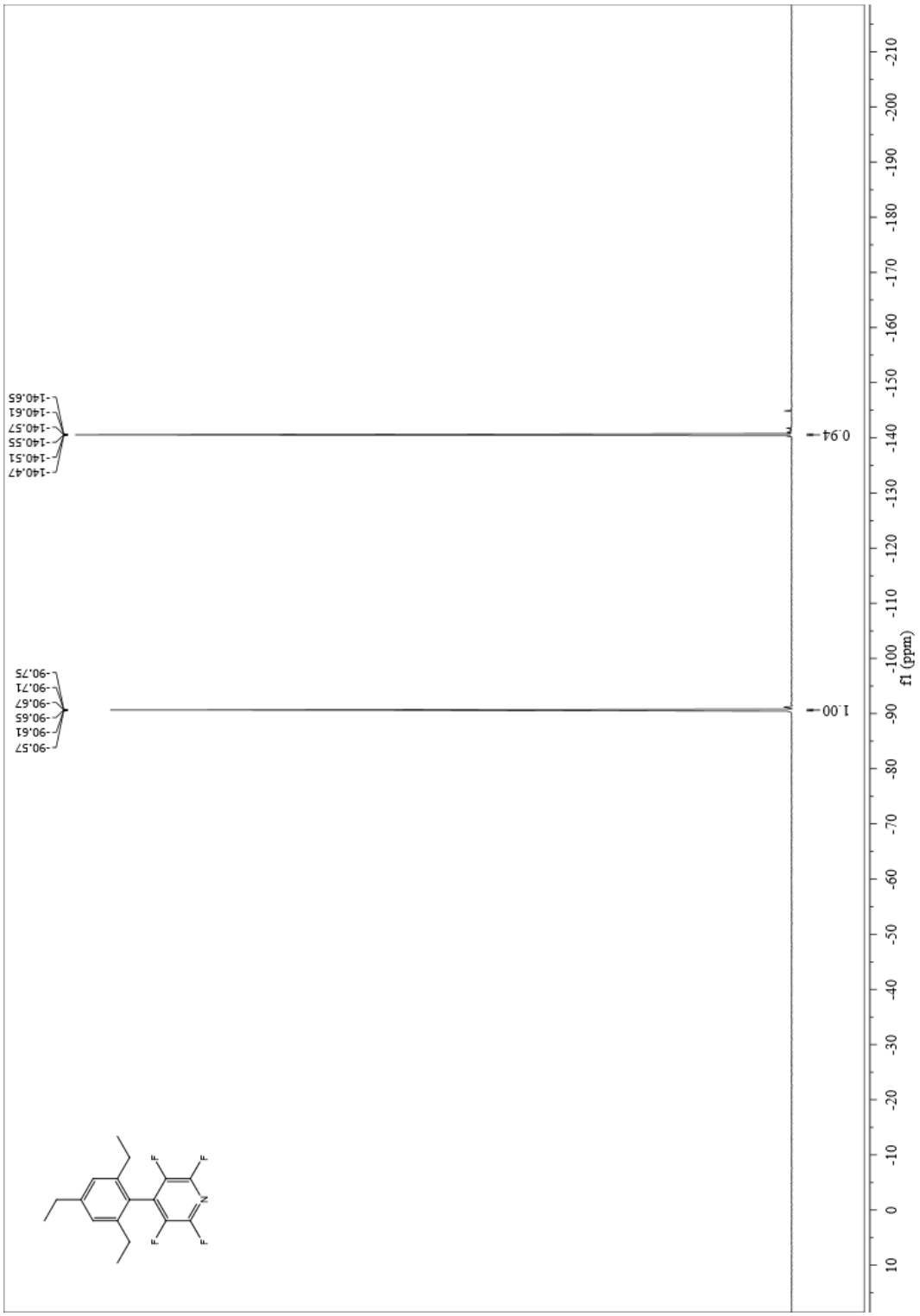


GC and MS of 3.6e (4-(2,4-di-tert-butyl-6-methylphenyl)-2,3,5,6-tetrafluoropyridine)

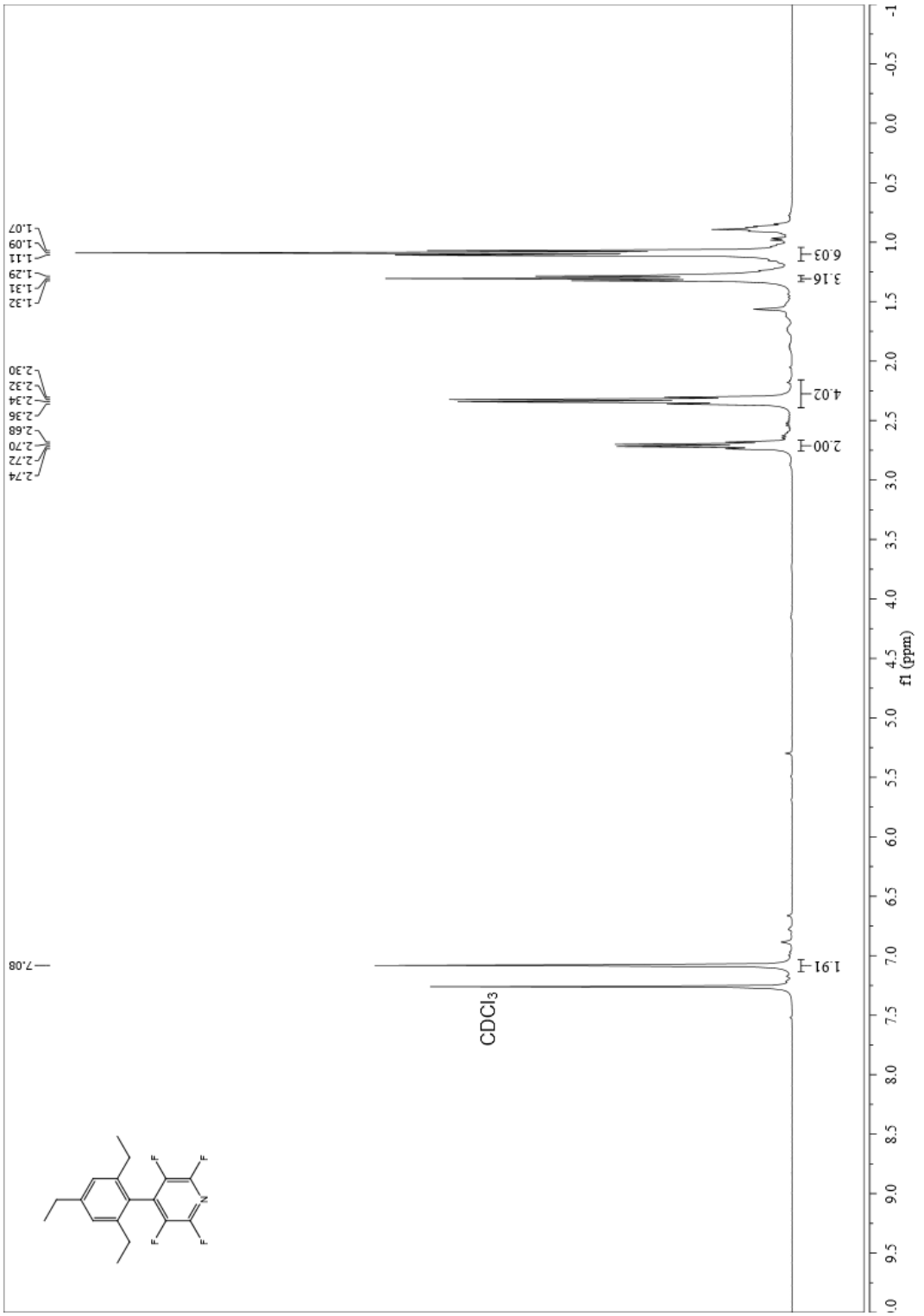




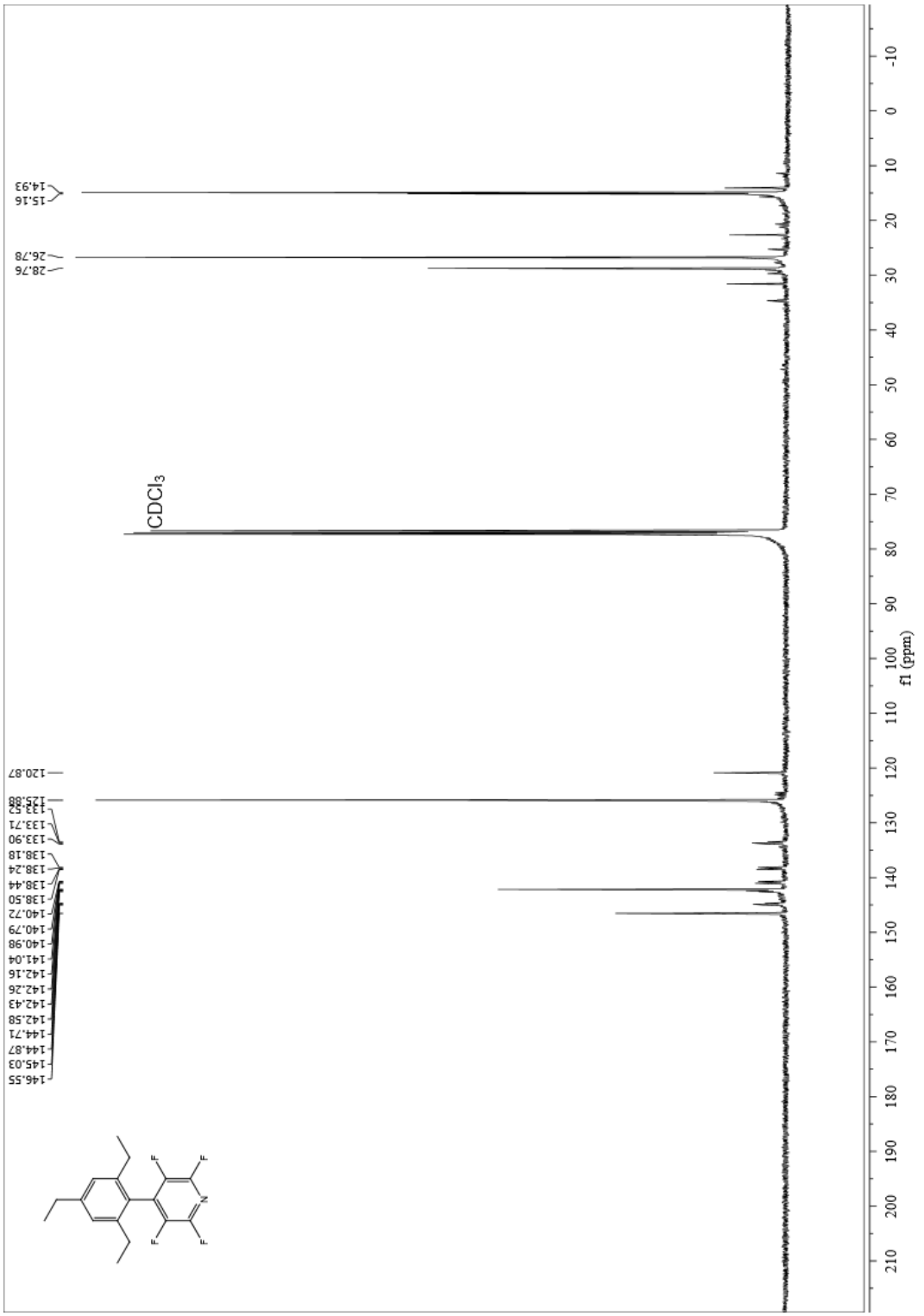
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6f (2,3,5,6-tetrafluoro-4-(2,4,6-triethylphenyl)pyridine



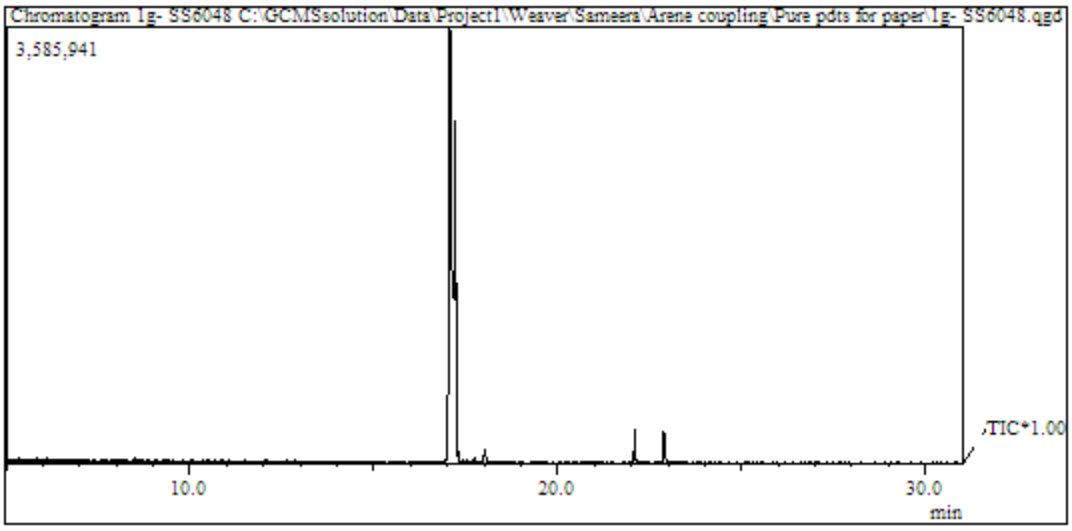
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6f (2,3,5,6-tetrafluoro-4-(2,4,6-triethylphenyl)pyridine

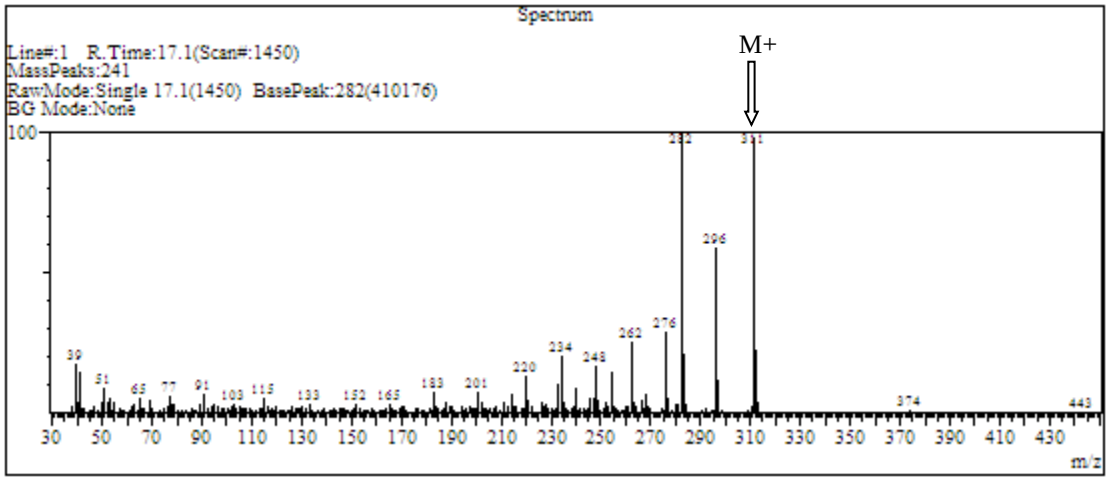


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6f (2,3,5,6-tetrafluoro-4-(2,4,6-triethylphenyl)pyridine

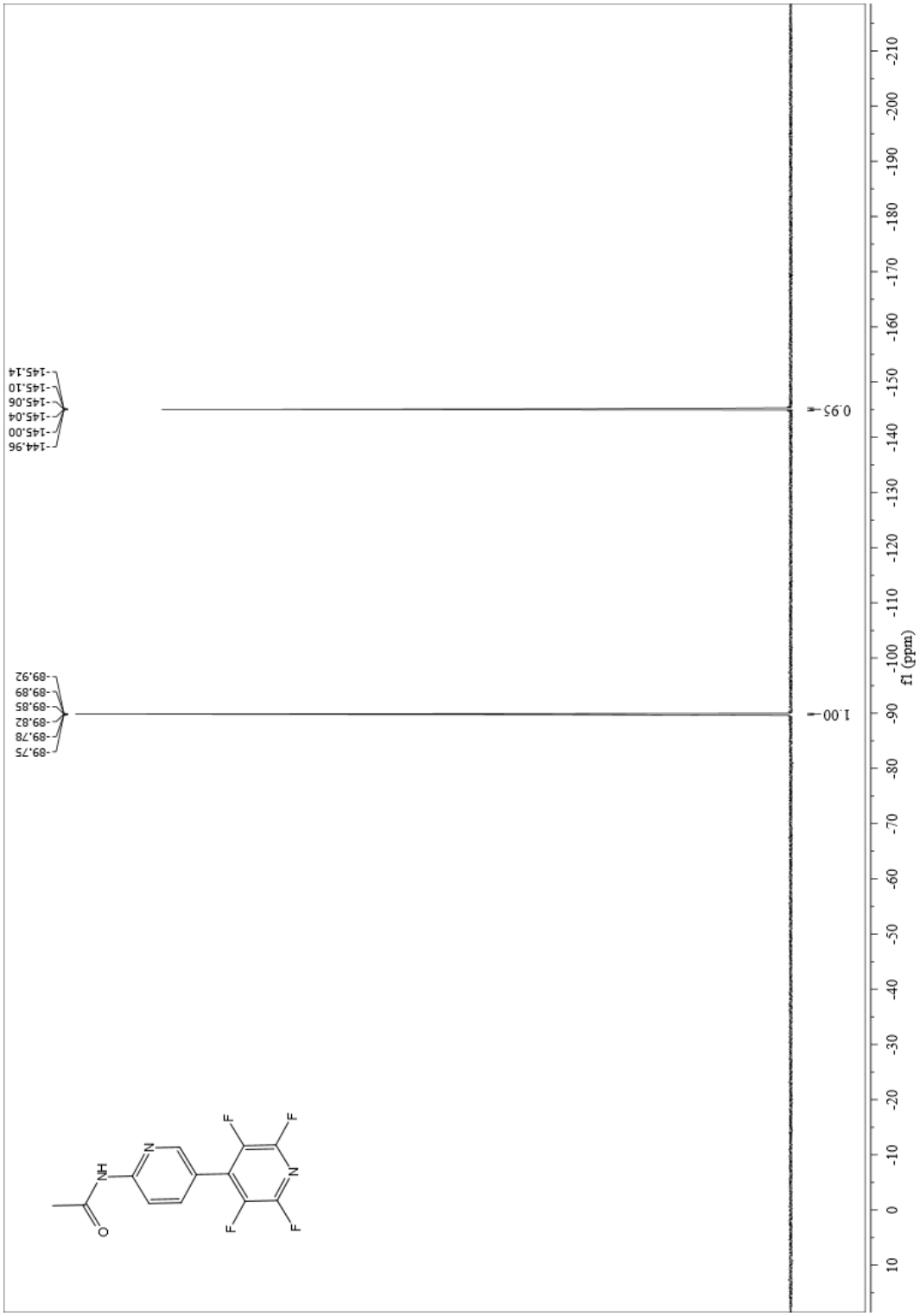


GC and MS of 3.6f (2,3,5,6-tetrafluoro-4-(2,4,6-triethylphenyl)pyridine

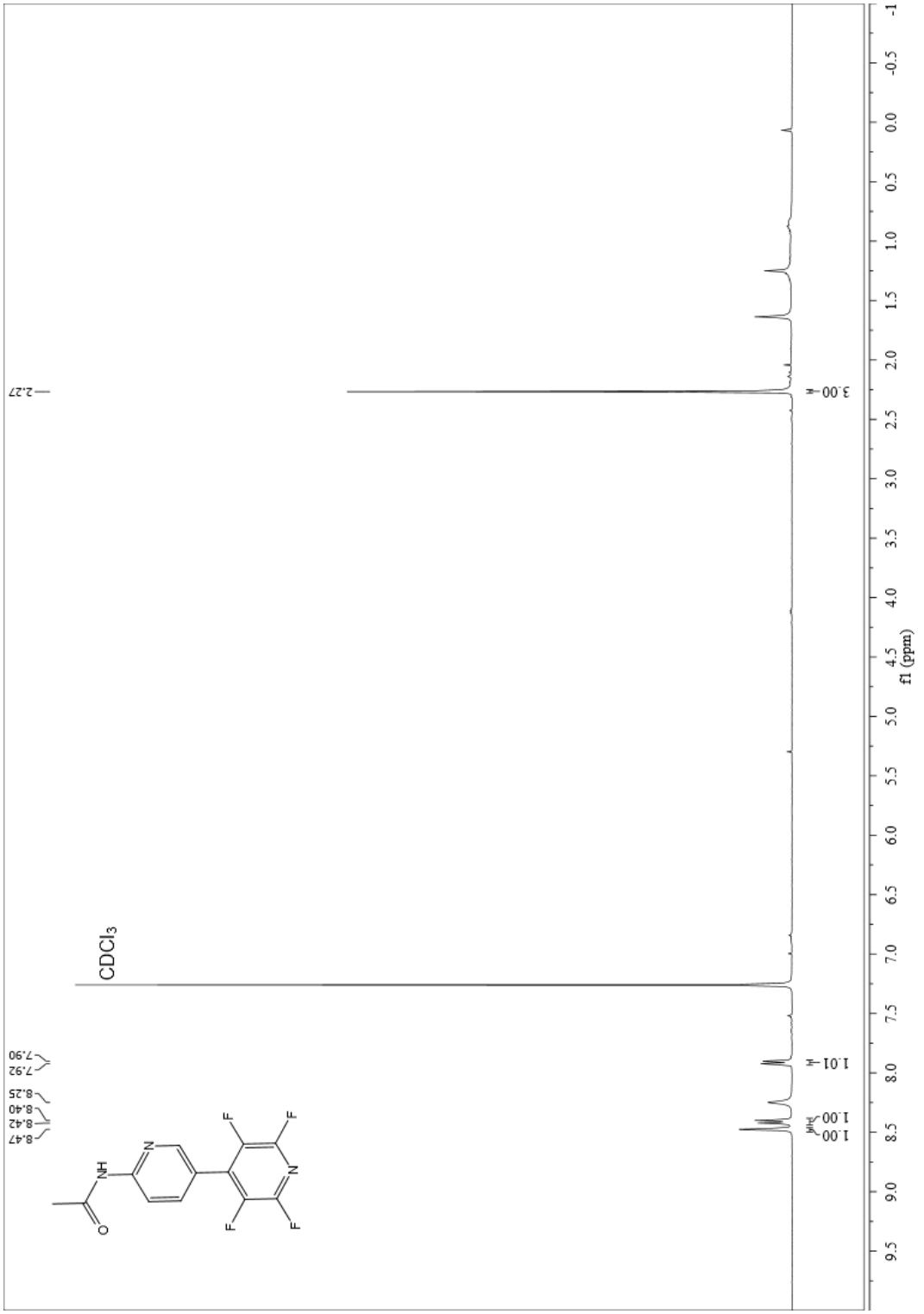




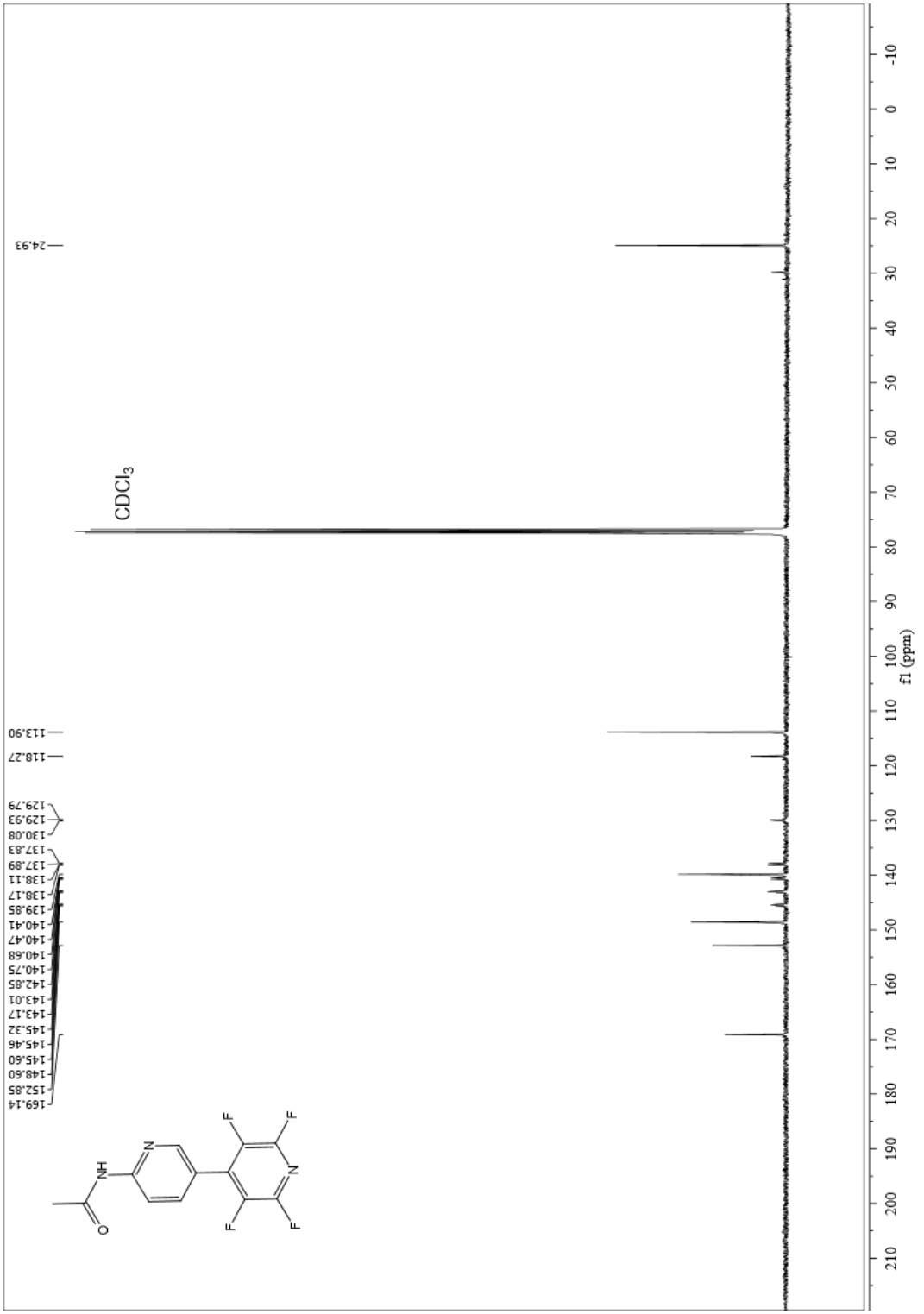
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6g-i (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-6-yl)acetamide)



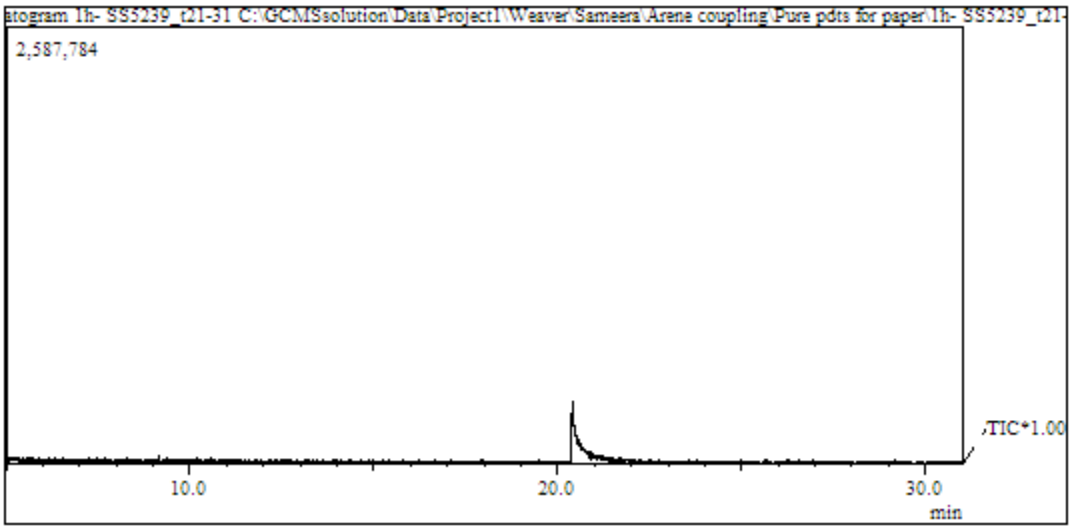
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6g-i (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-6-yl)acetamide)

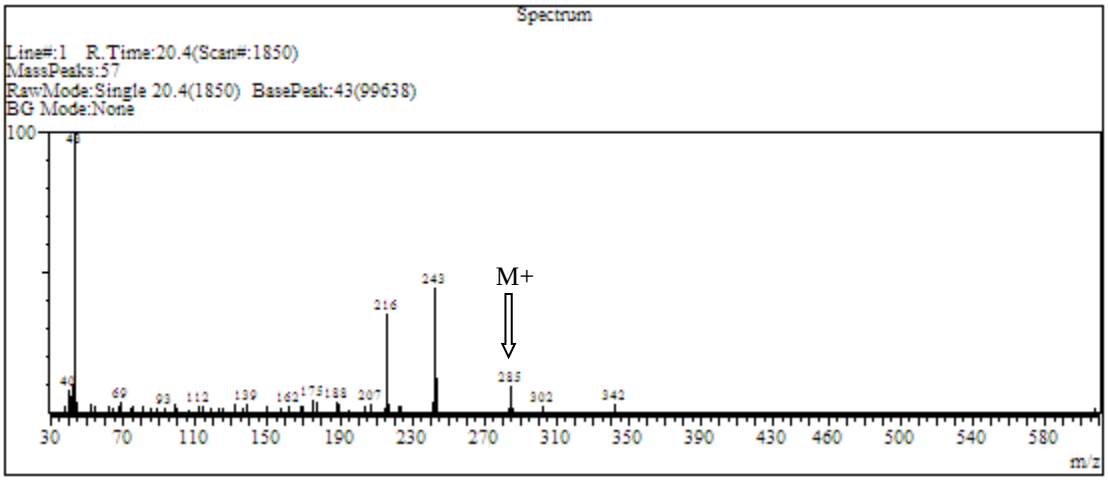


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6g-i (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-6-yl)acetamide)

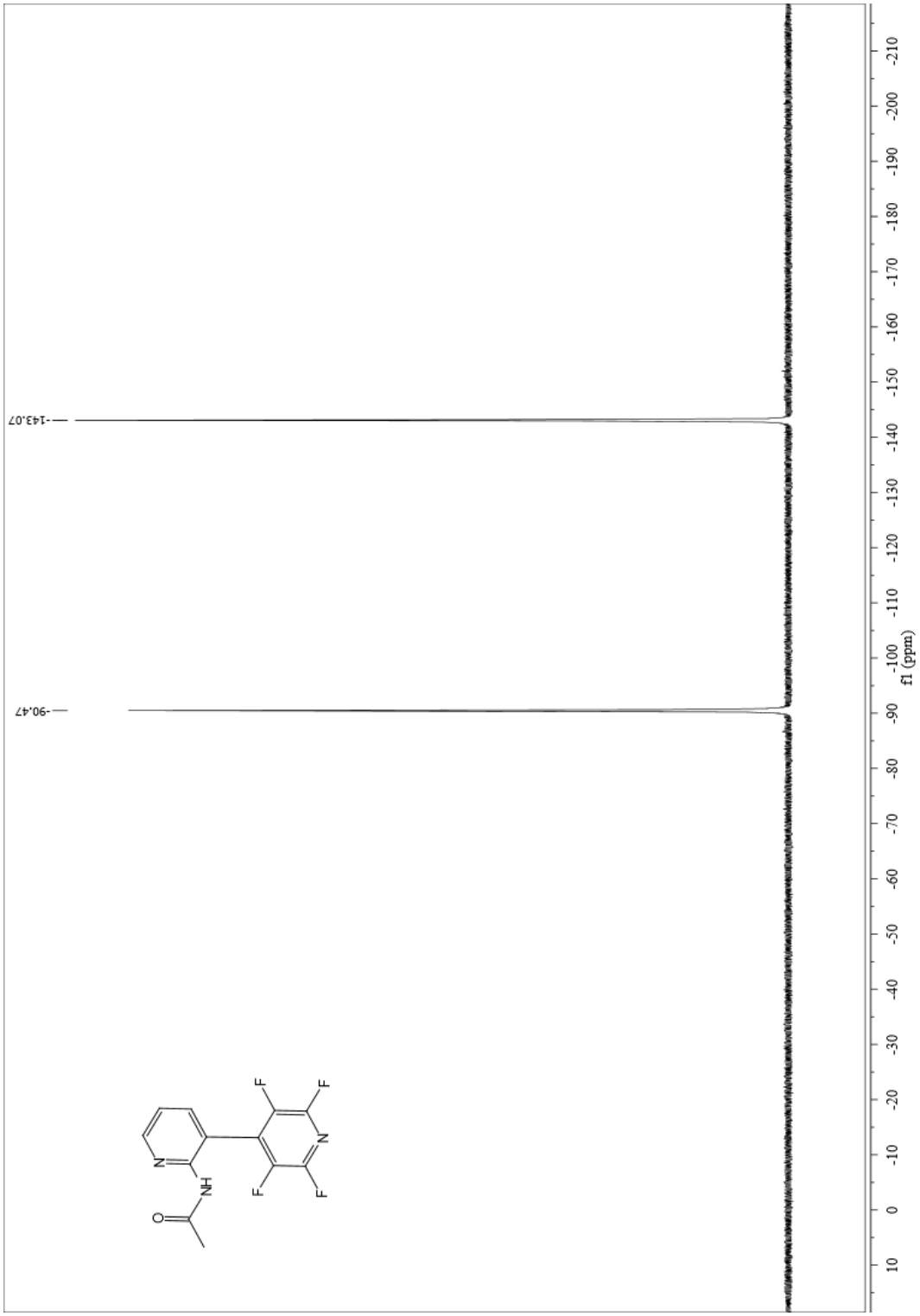


GC and MS of 7a-i (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-6-yl)acetamide)

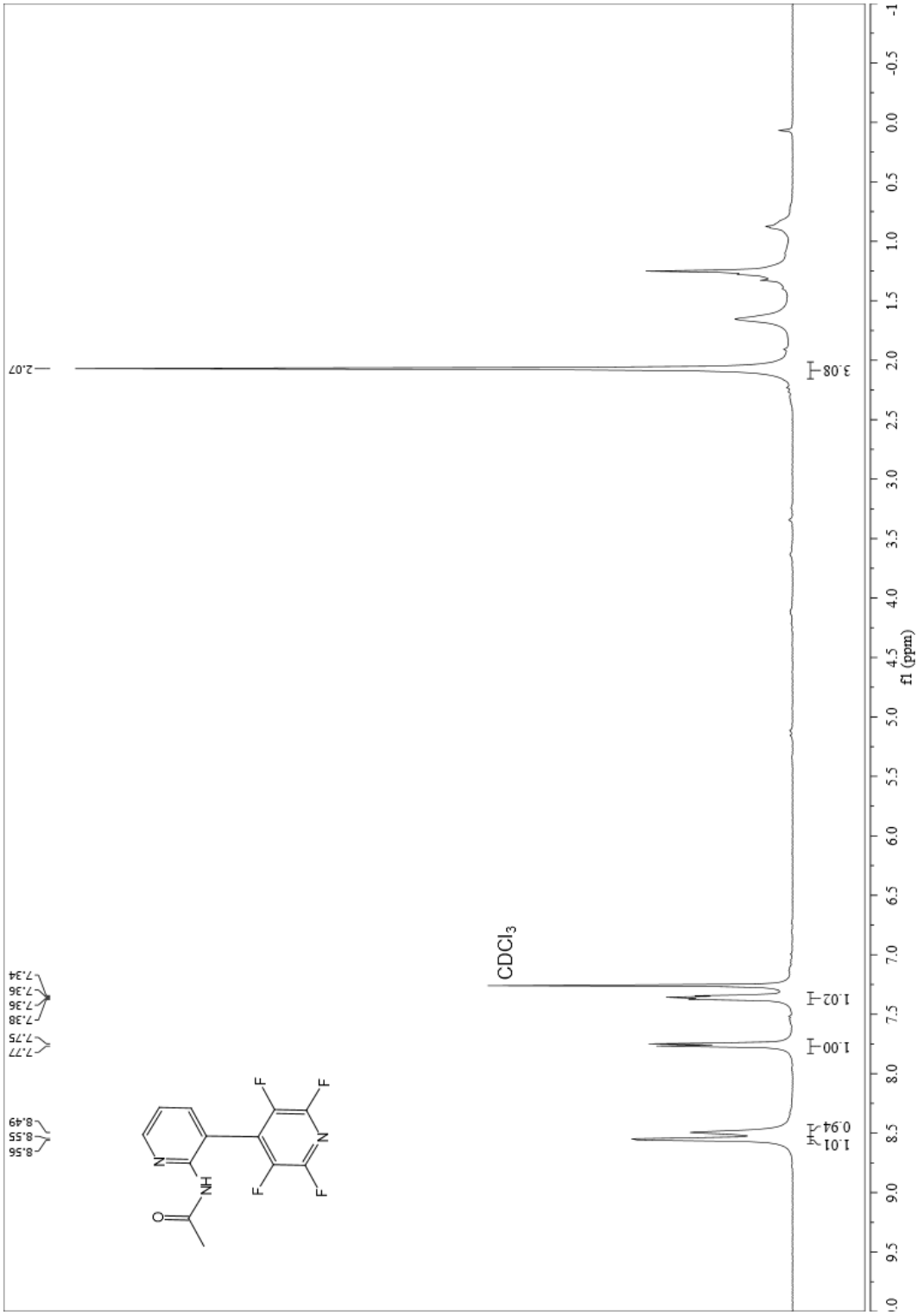




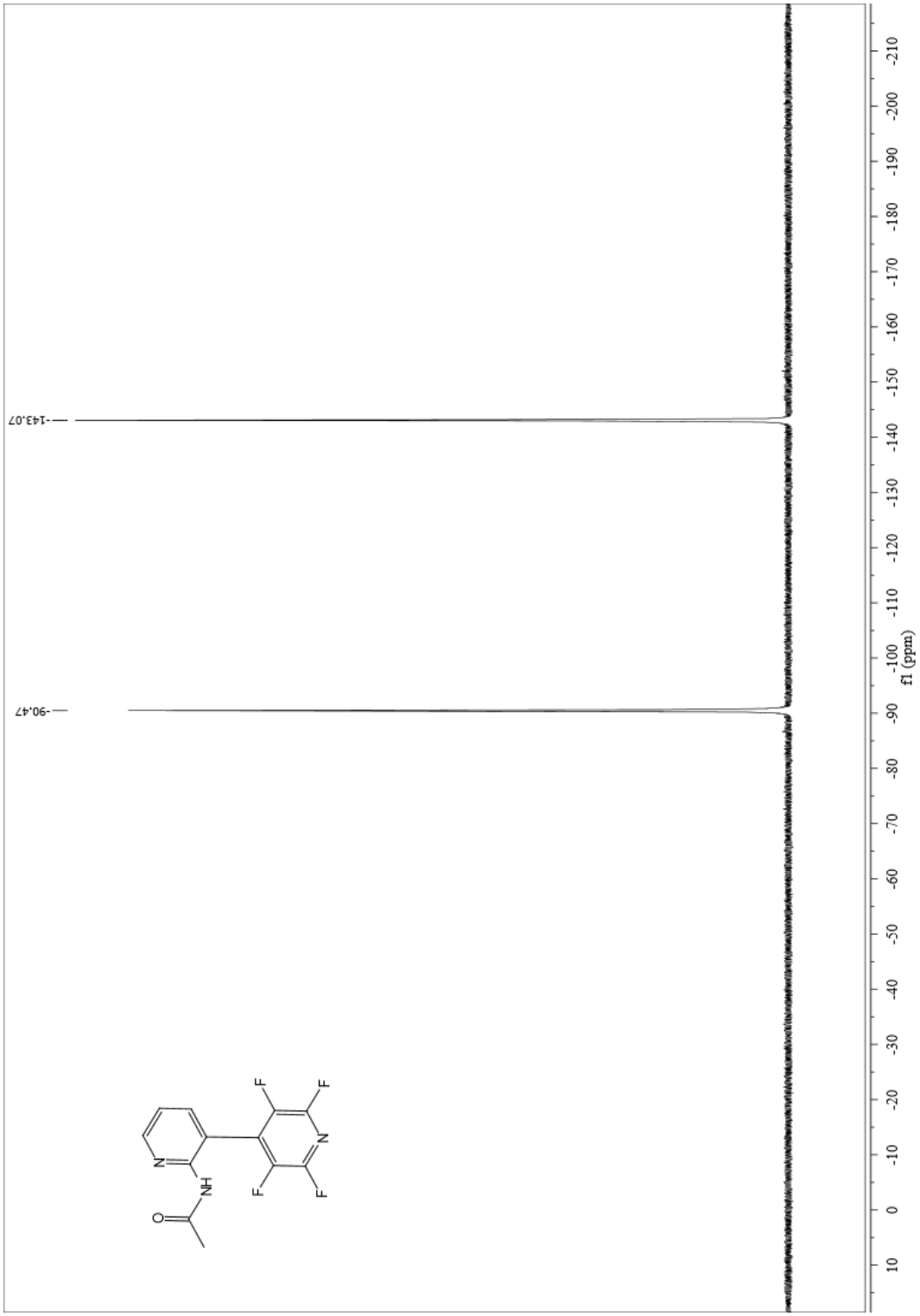
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6g-ii (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-2-yl)acetamide)



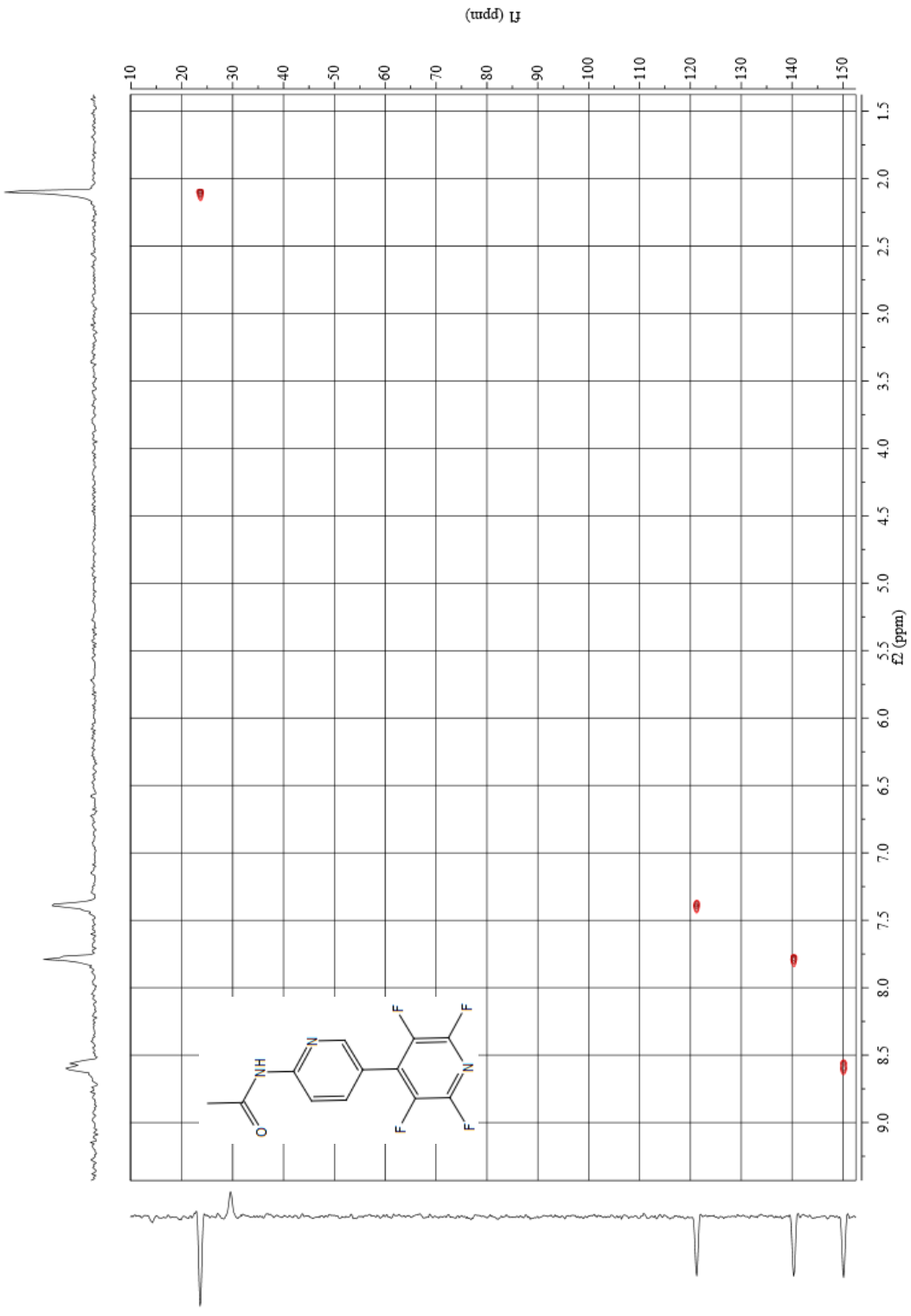
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6g-ii (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-2-yl)acetamide)



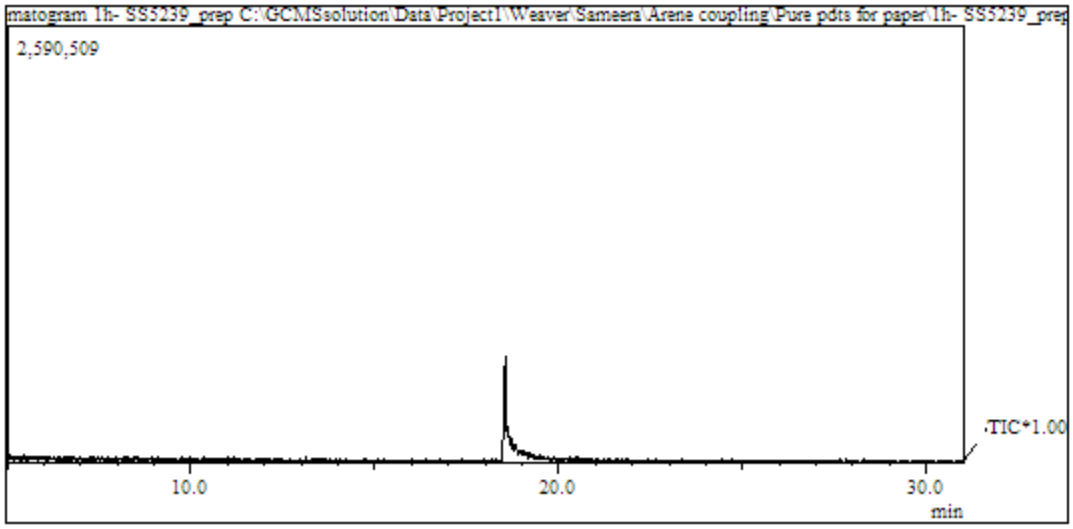
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6g-ii (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-2-yl)acetamide)

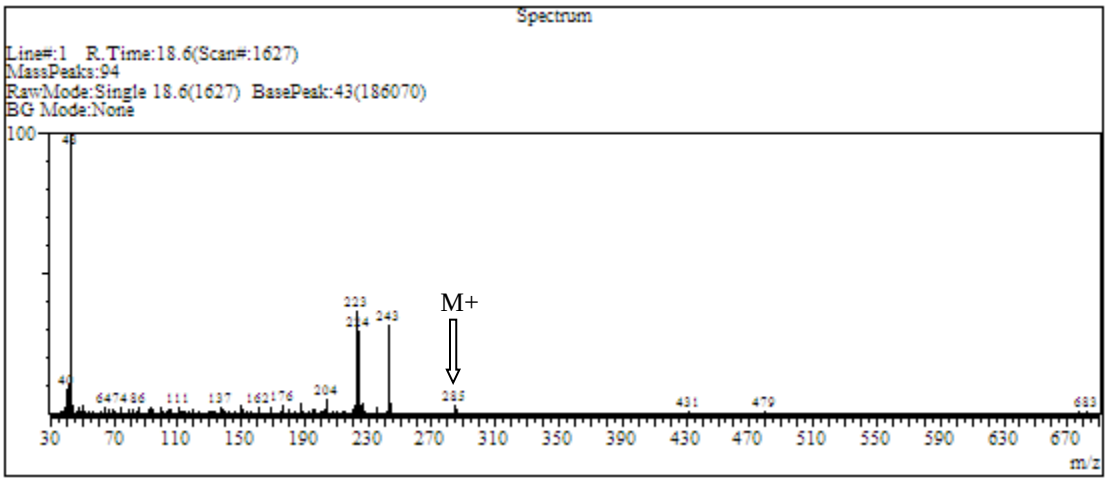


HSQC NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6g-ii (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-2-yl)acetamide)

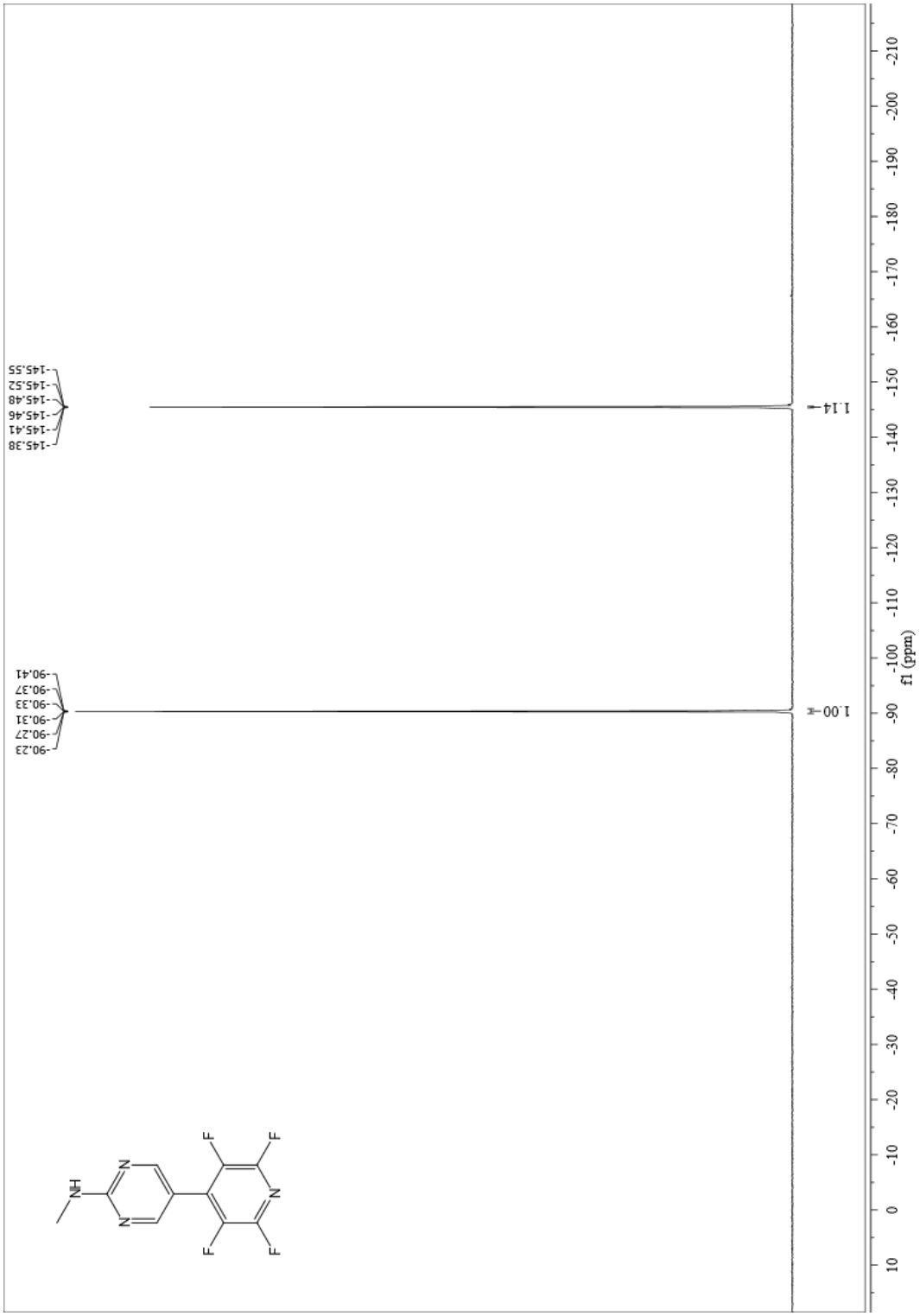


GC and MS of 3.6g-ii (N-(2',3',5',6'-tetrafluoro-[3,4'-bipyridin]-2-yl)acetamide)

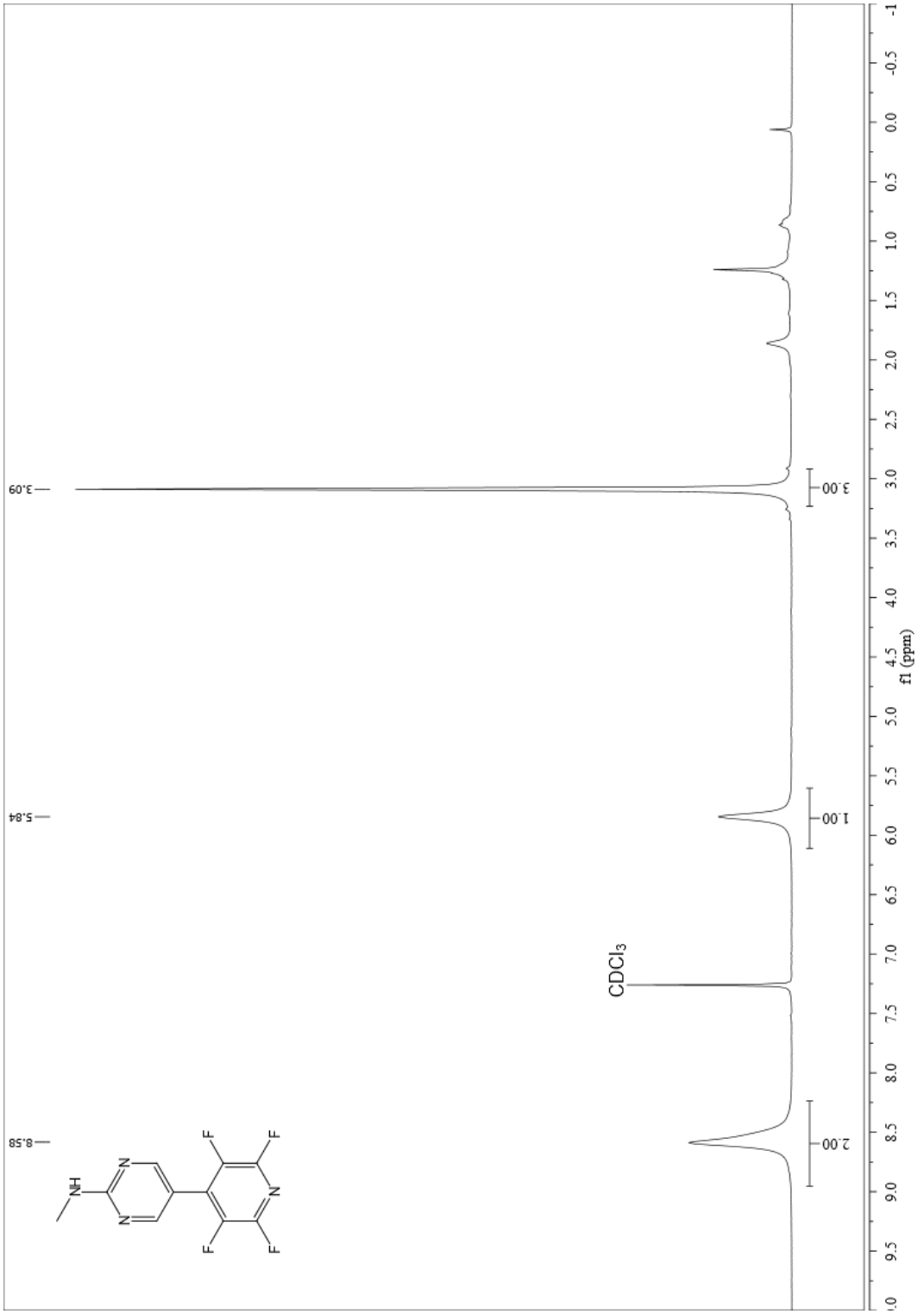




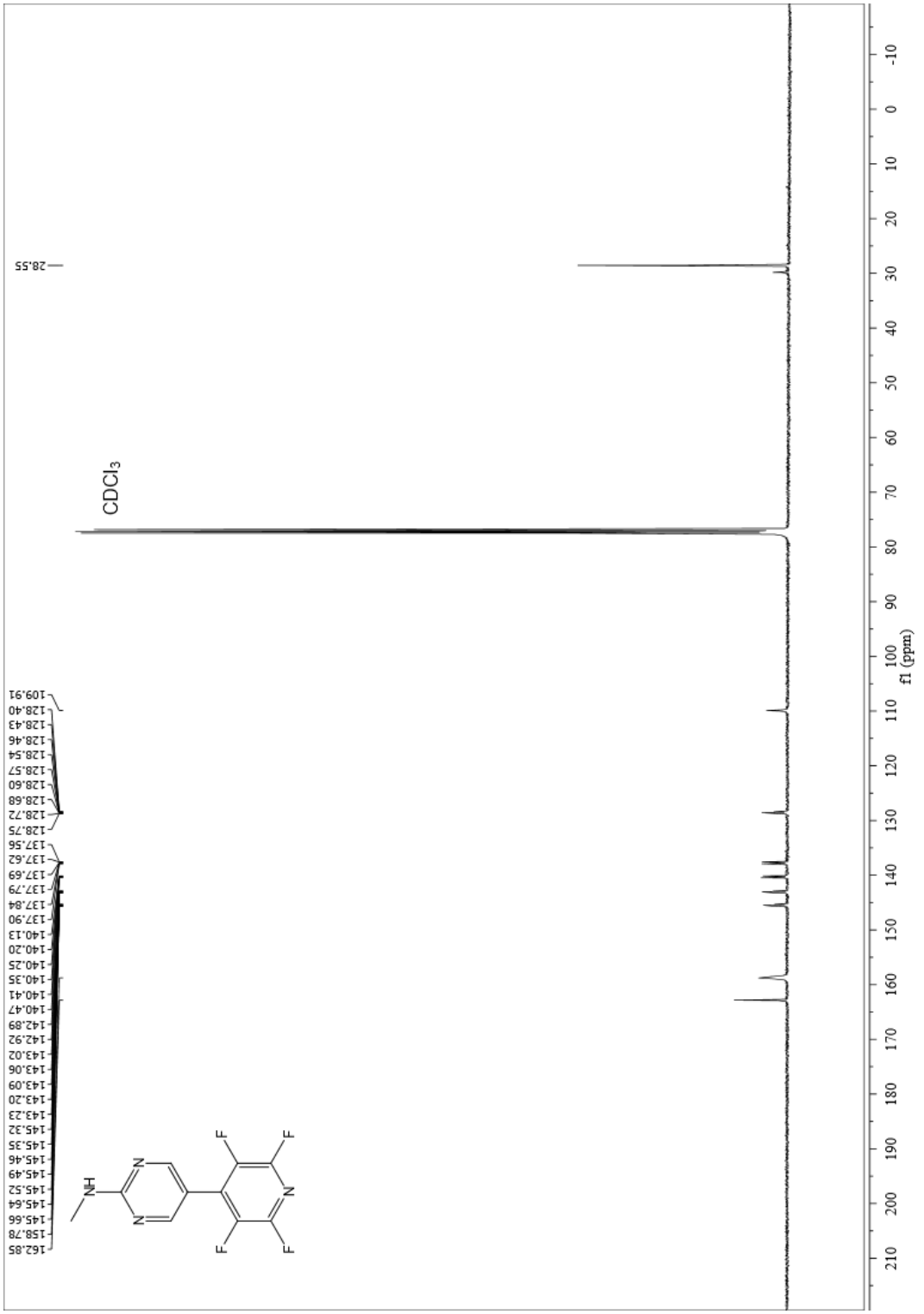
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6h (N-methyl-5-(perfluoropyridin-4-yl)pyrimidin-2-amine)



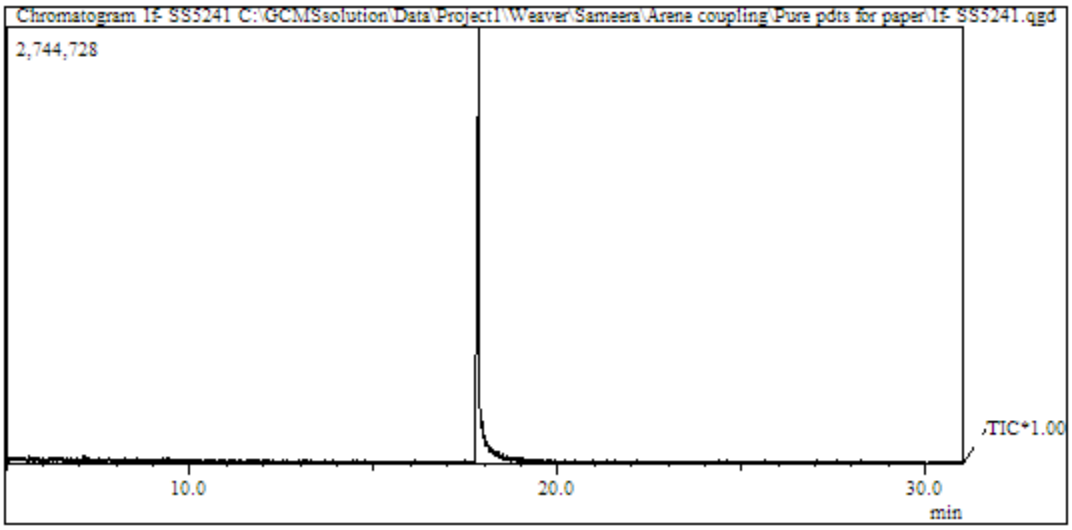
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6h (N-methyl-5-(perfluoropyridin-4-yl)pyrimidin-2-amine)

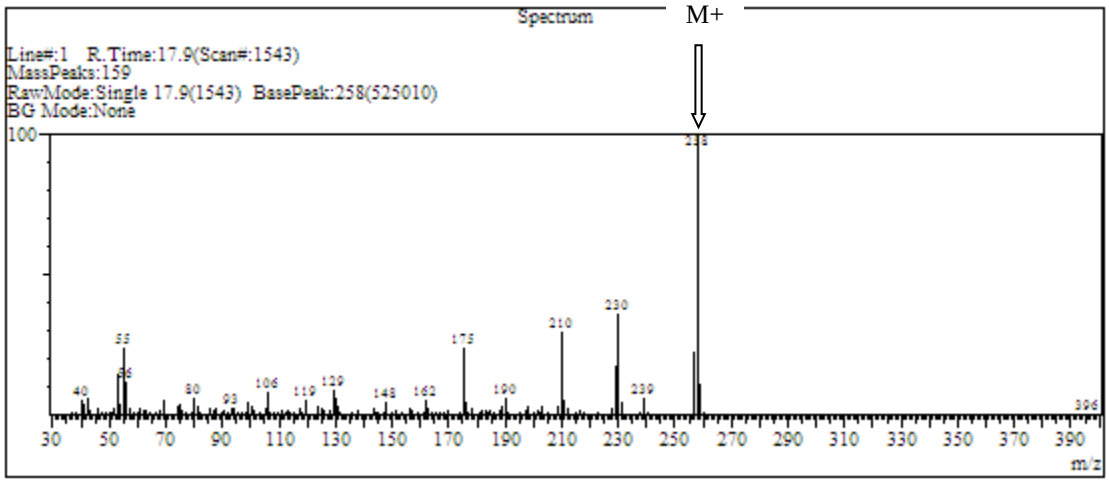


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6h (N-methyl-5-(perfluoropyridin-4-yl)pyrimidin-2-amine)

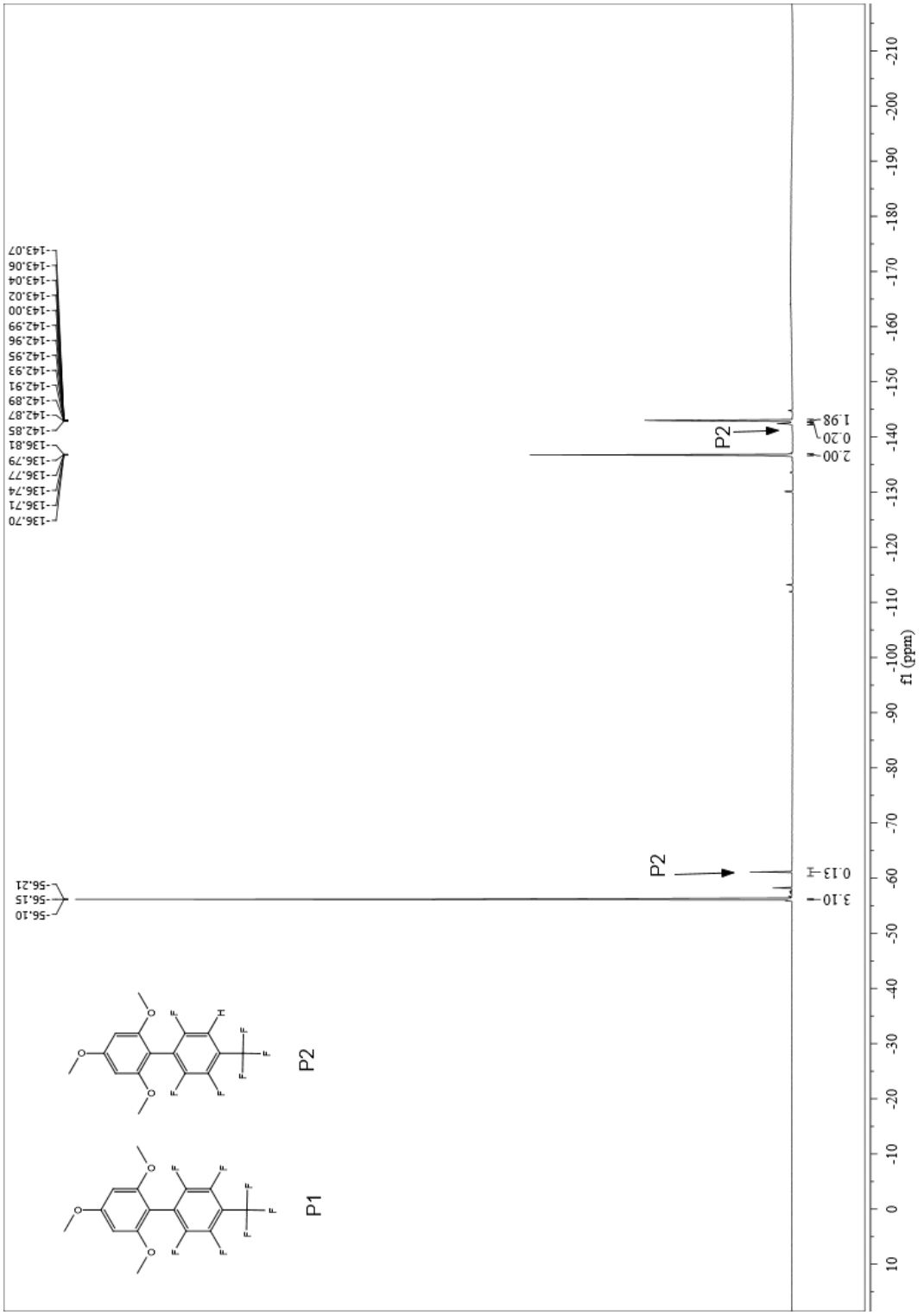


GC and MS of 3.6h (N-methyl-5-(perfluoropyridin-4-yl)pyrimidin-2-amine)

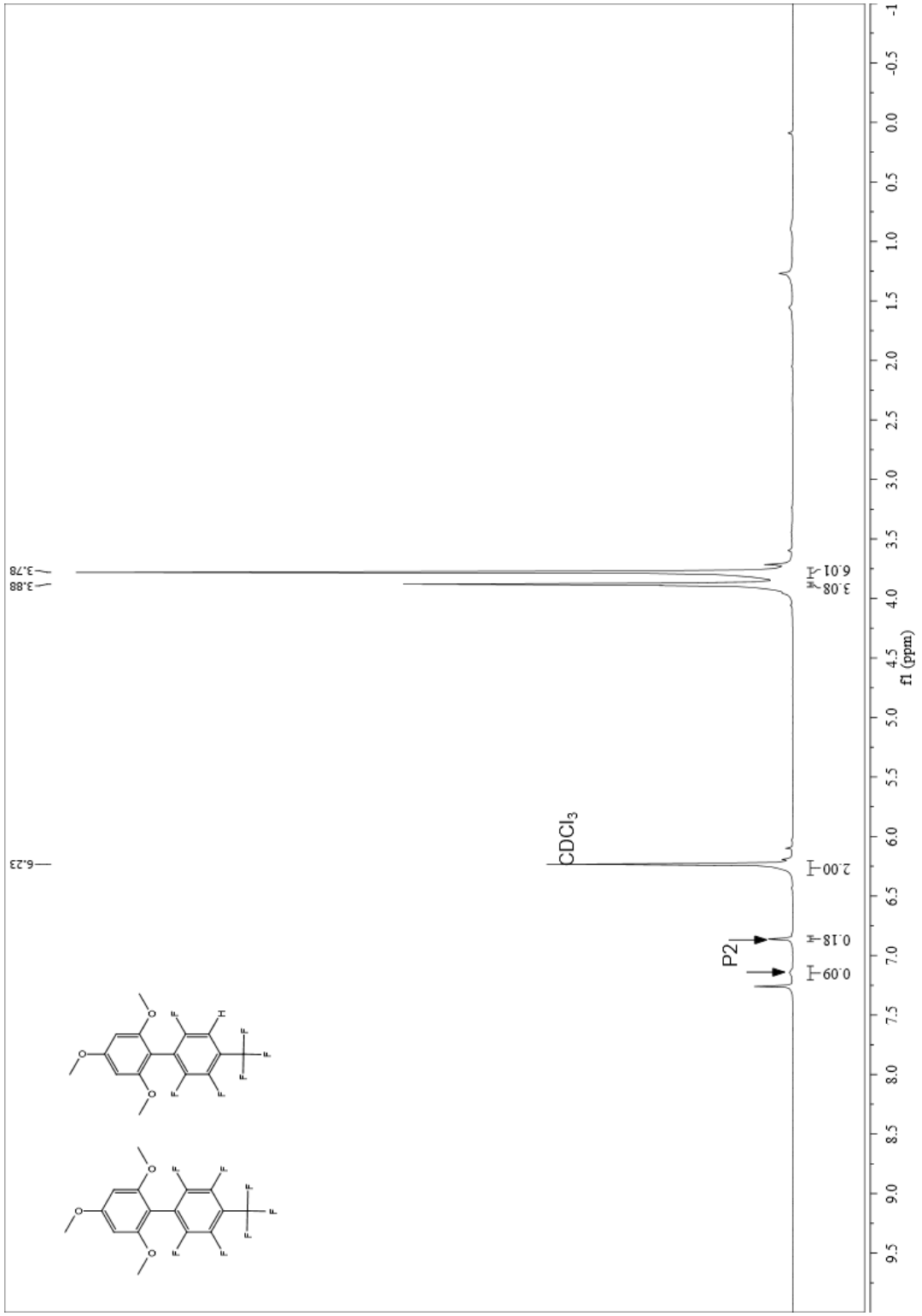




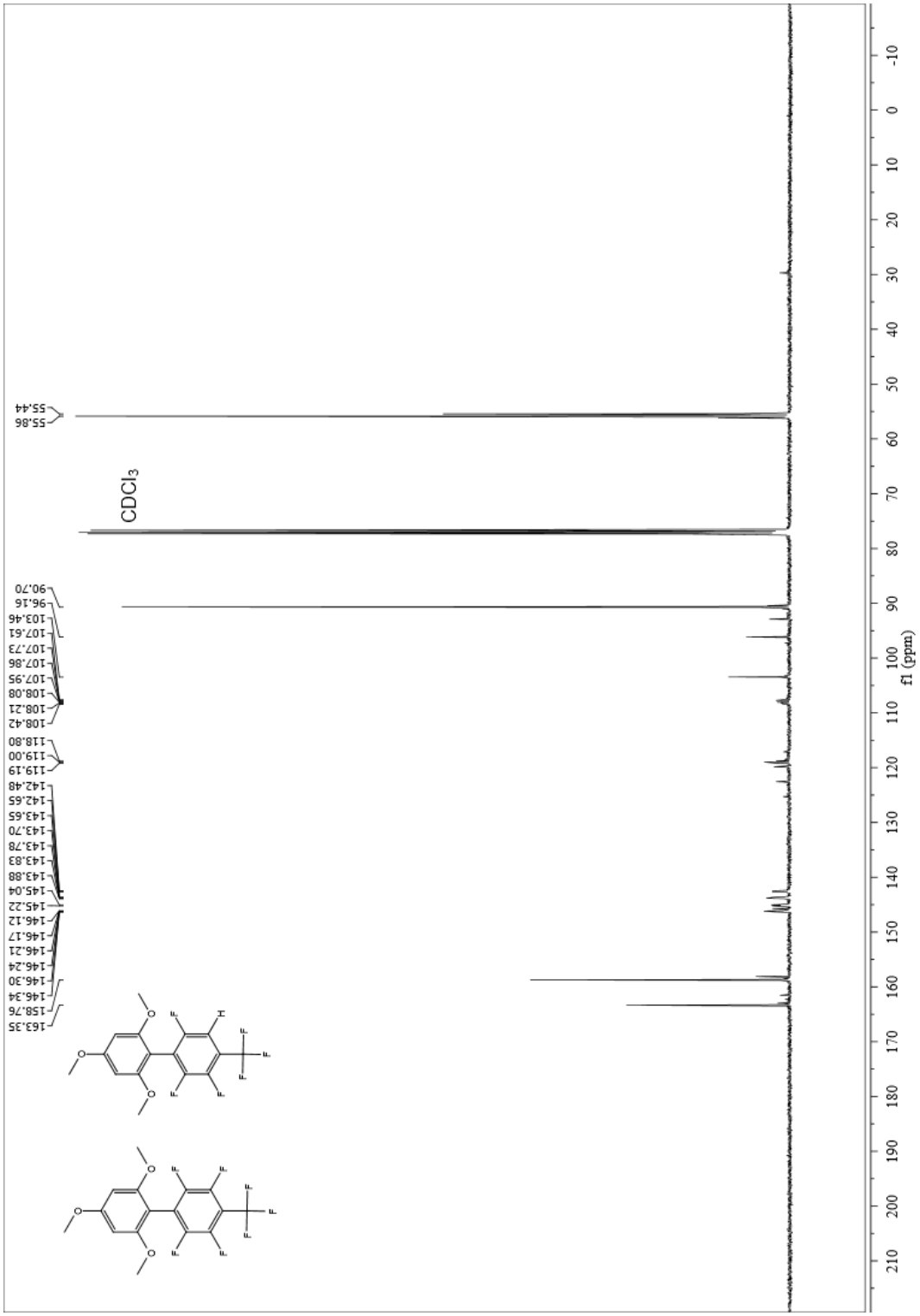
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6i (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-4-(trifluoromethyl)-1,1'-biphenyl)



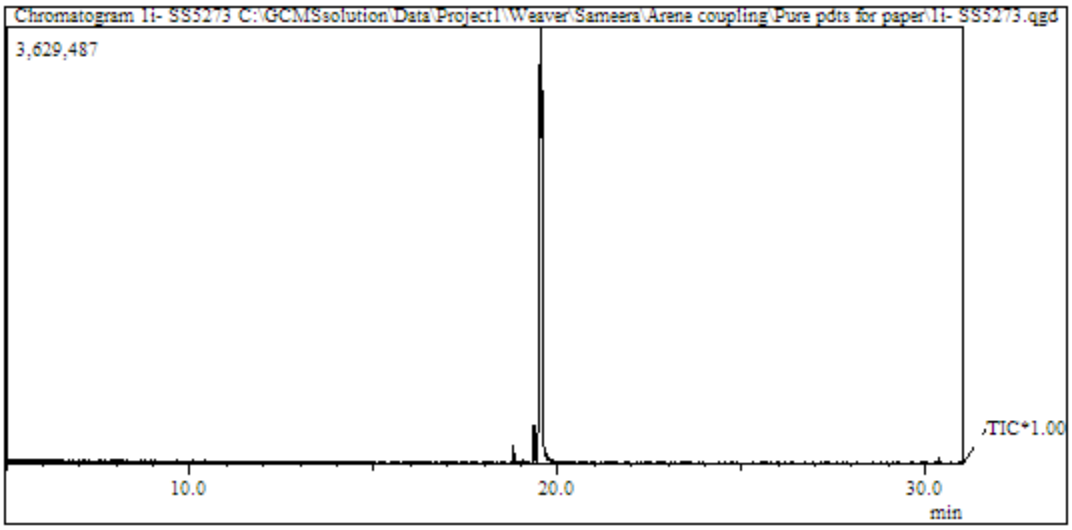
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6i (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-4-(trifluoromethyl)-1,1'-biphenyl)

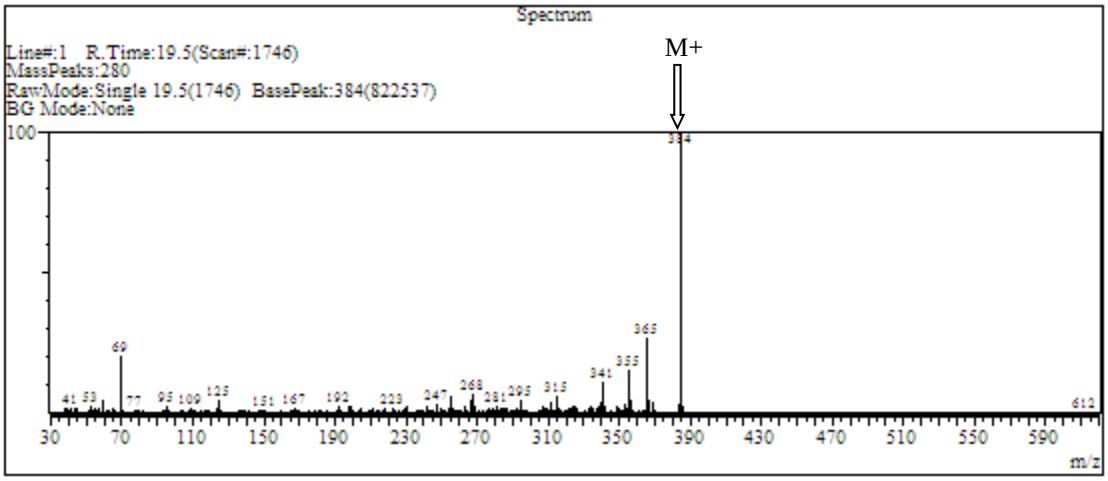


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6i (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-4-(trifluoromethyl)-1,1'-biphenyl)

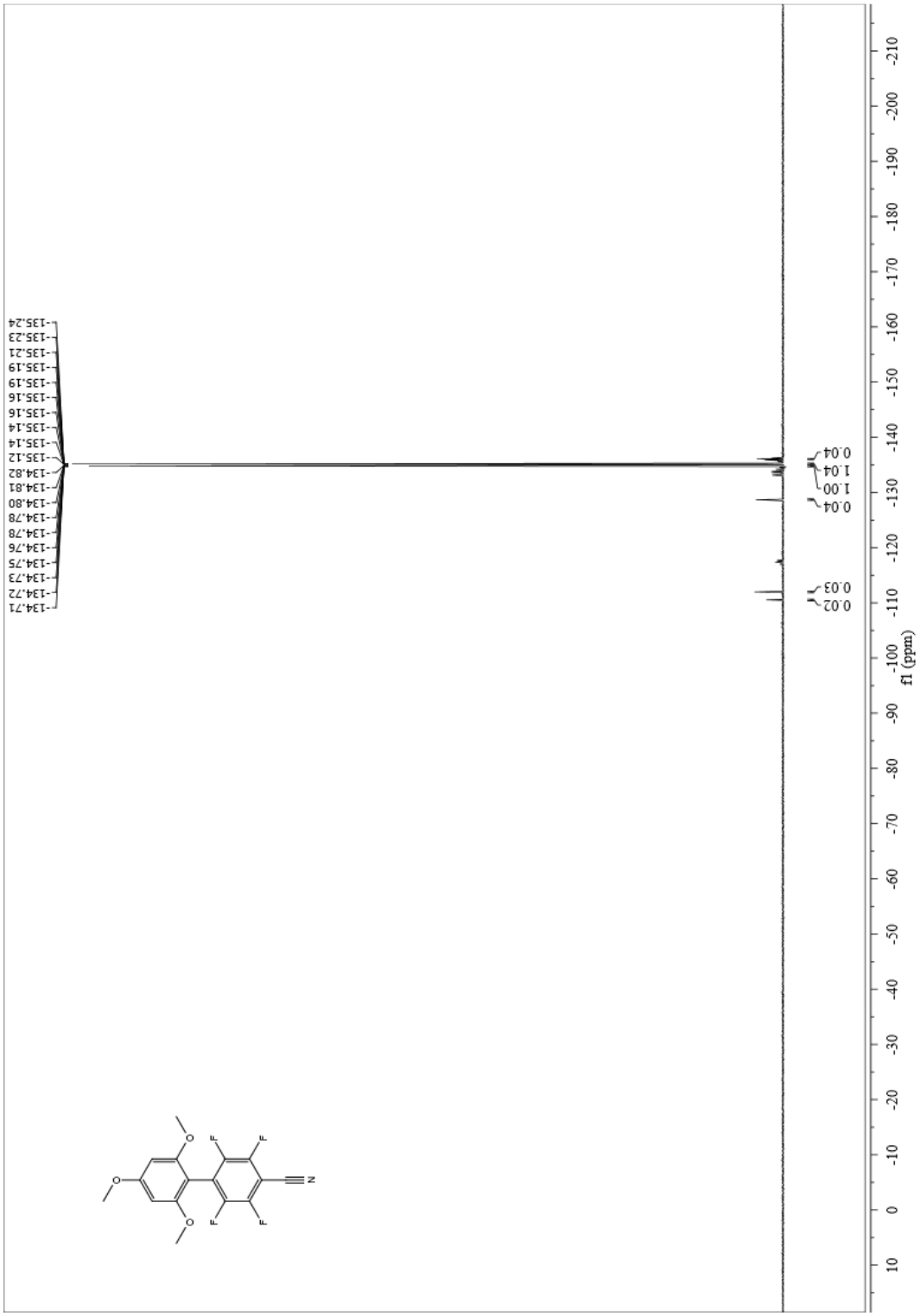


GC and MS of 3.6i (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-4-(trifluoromethyl)-1,1'-biphenyl)

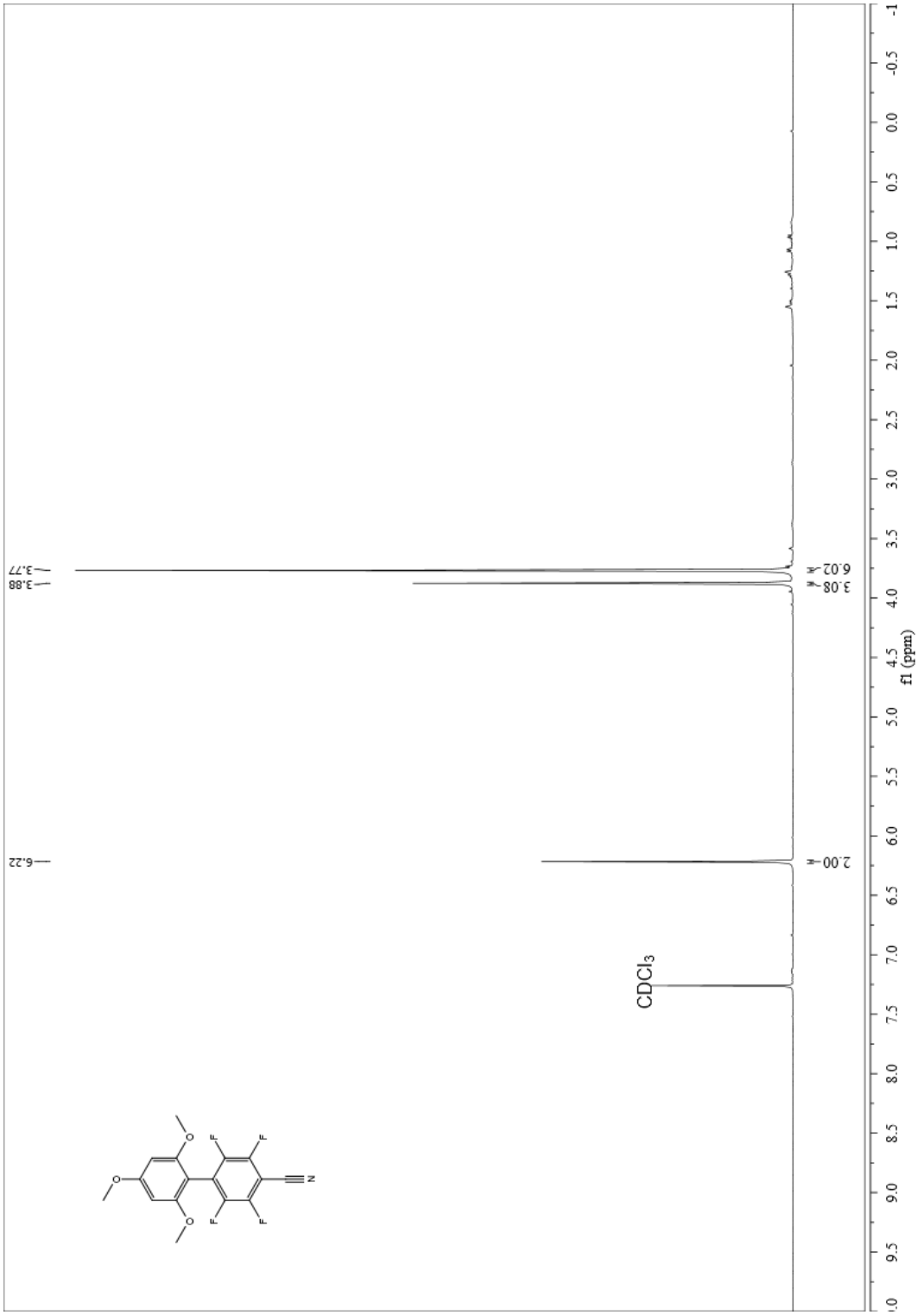




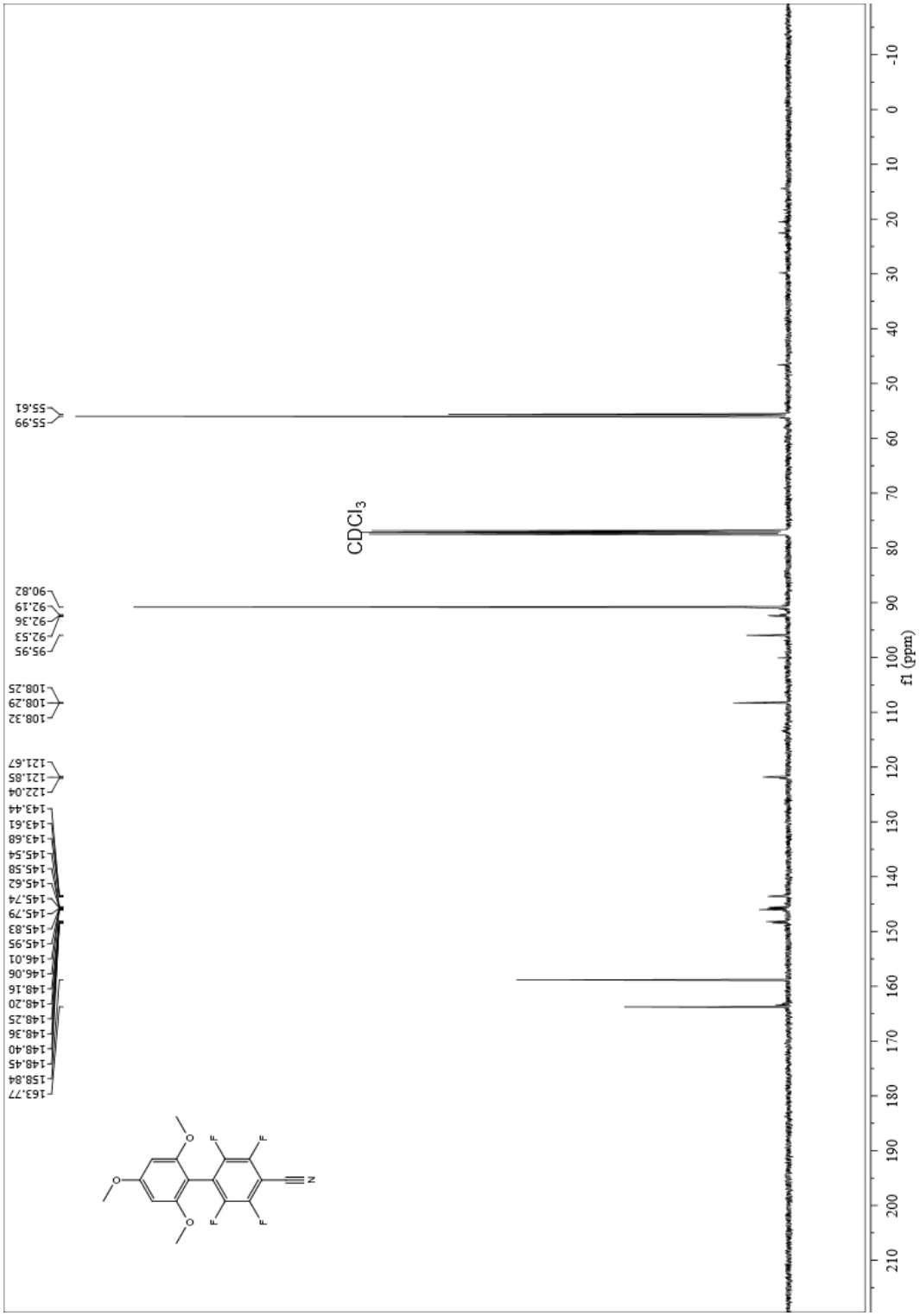
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6j (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carbonitrile)



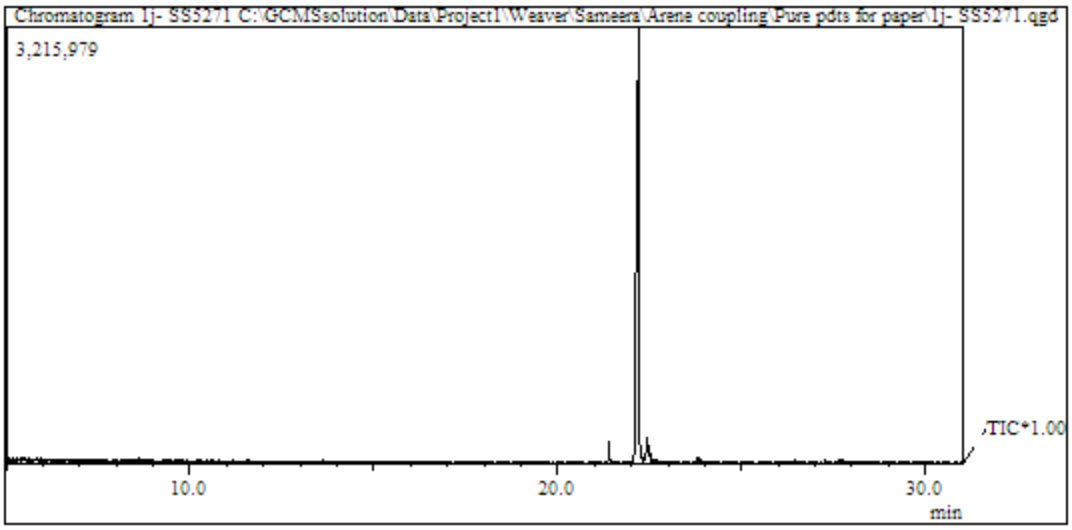
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6j (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carbonitrile)

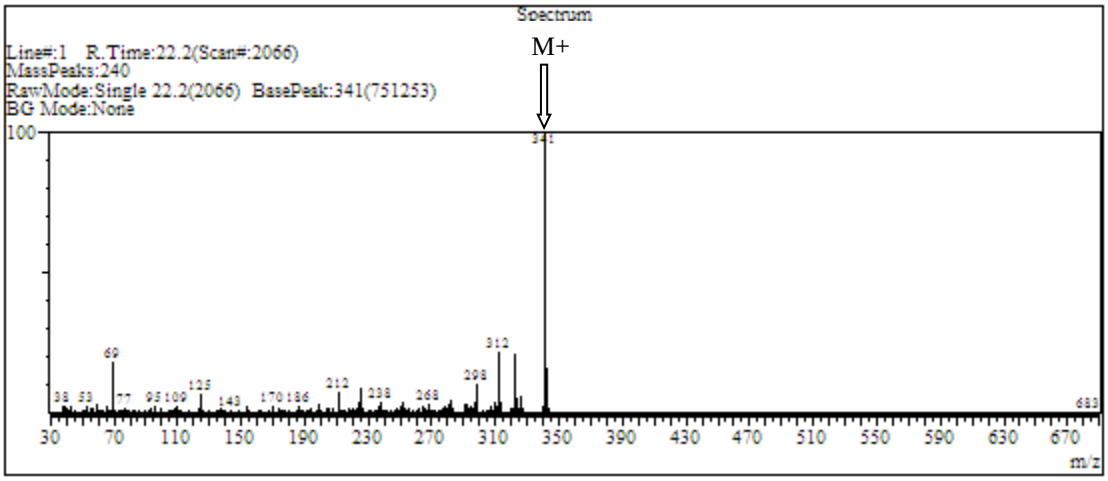


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6j (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carbonitrile)

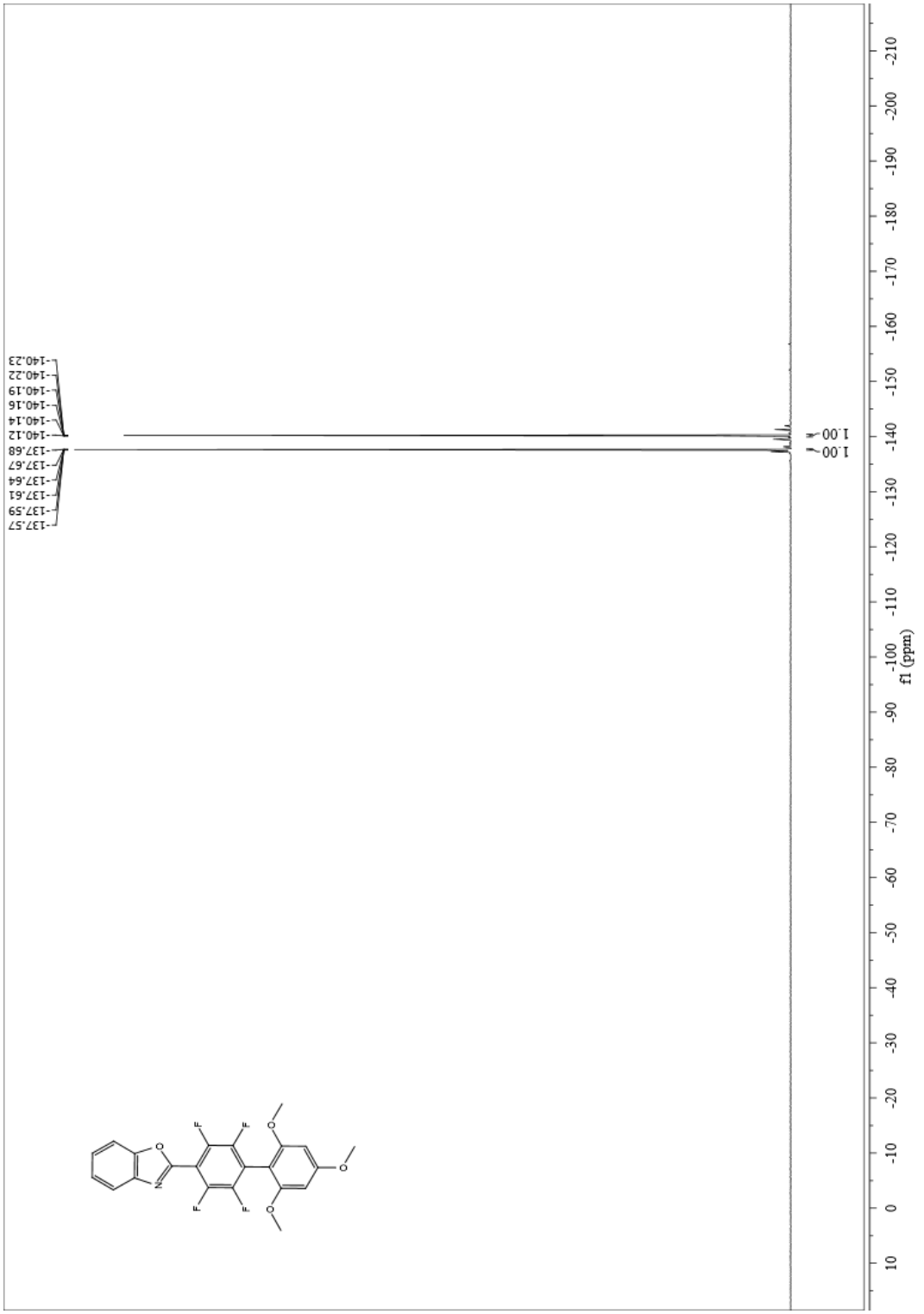


GC and MS of 3.6j (2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carbonitrile)

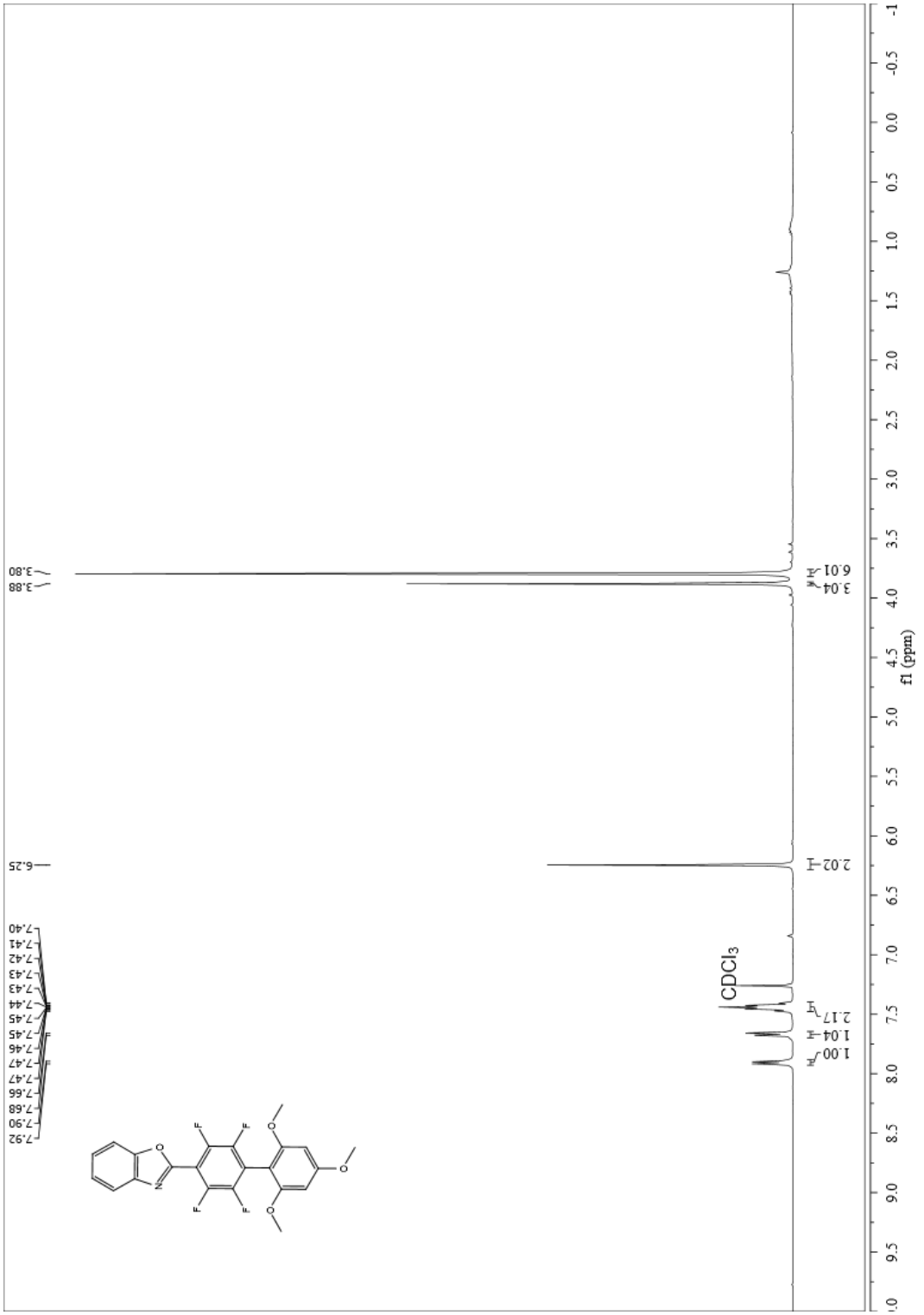




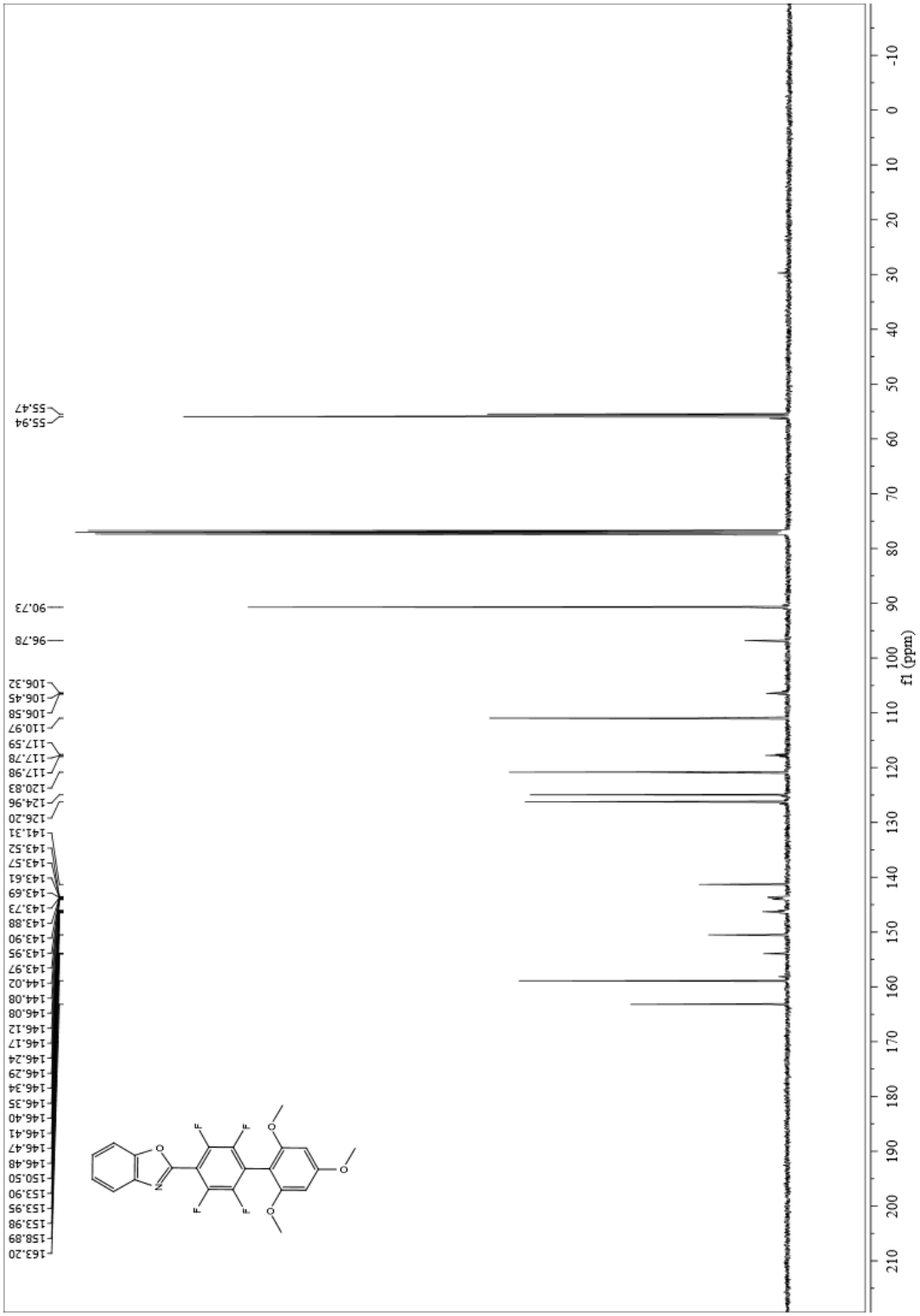
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6k (2-(2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-yl)benzo[d]oxazole)



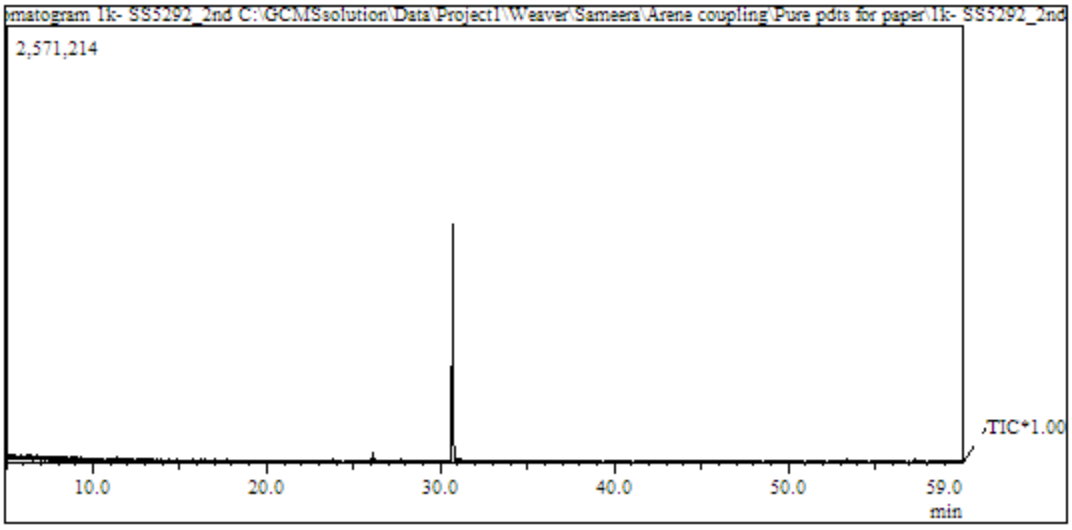
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6k (2-(2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-yl)benzo[d]oxazole)

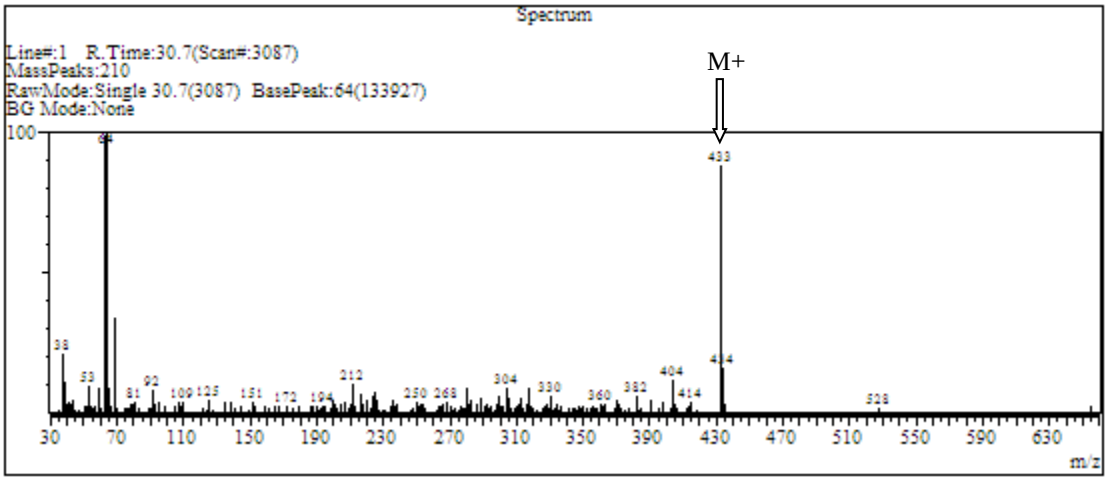


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6k (2-(2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-yl)benzo[d]oxazole)

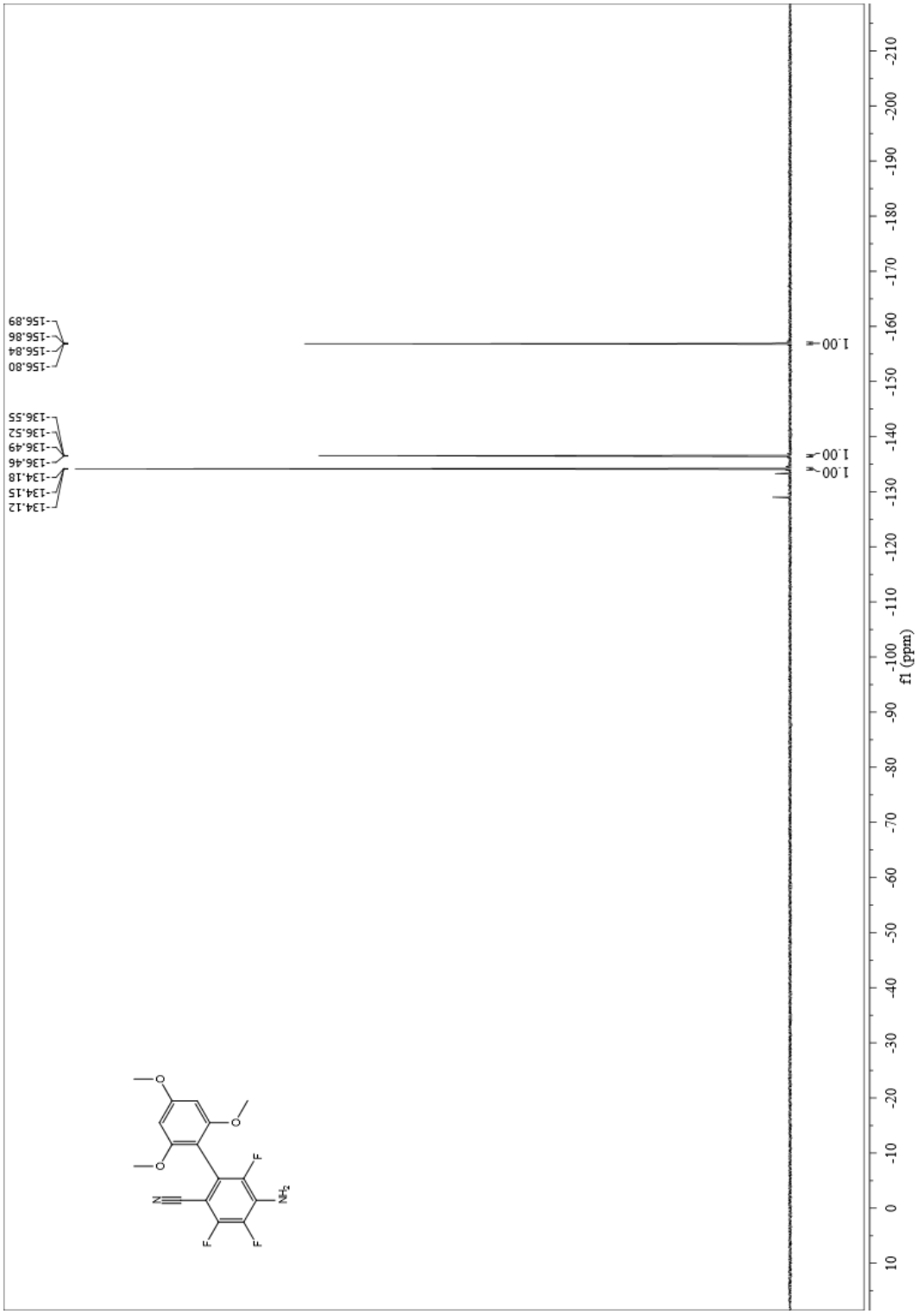


GC and MS of 3.6k (2-(2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-yl)benzo[d]oxazole)

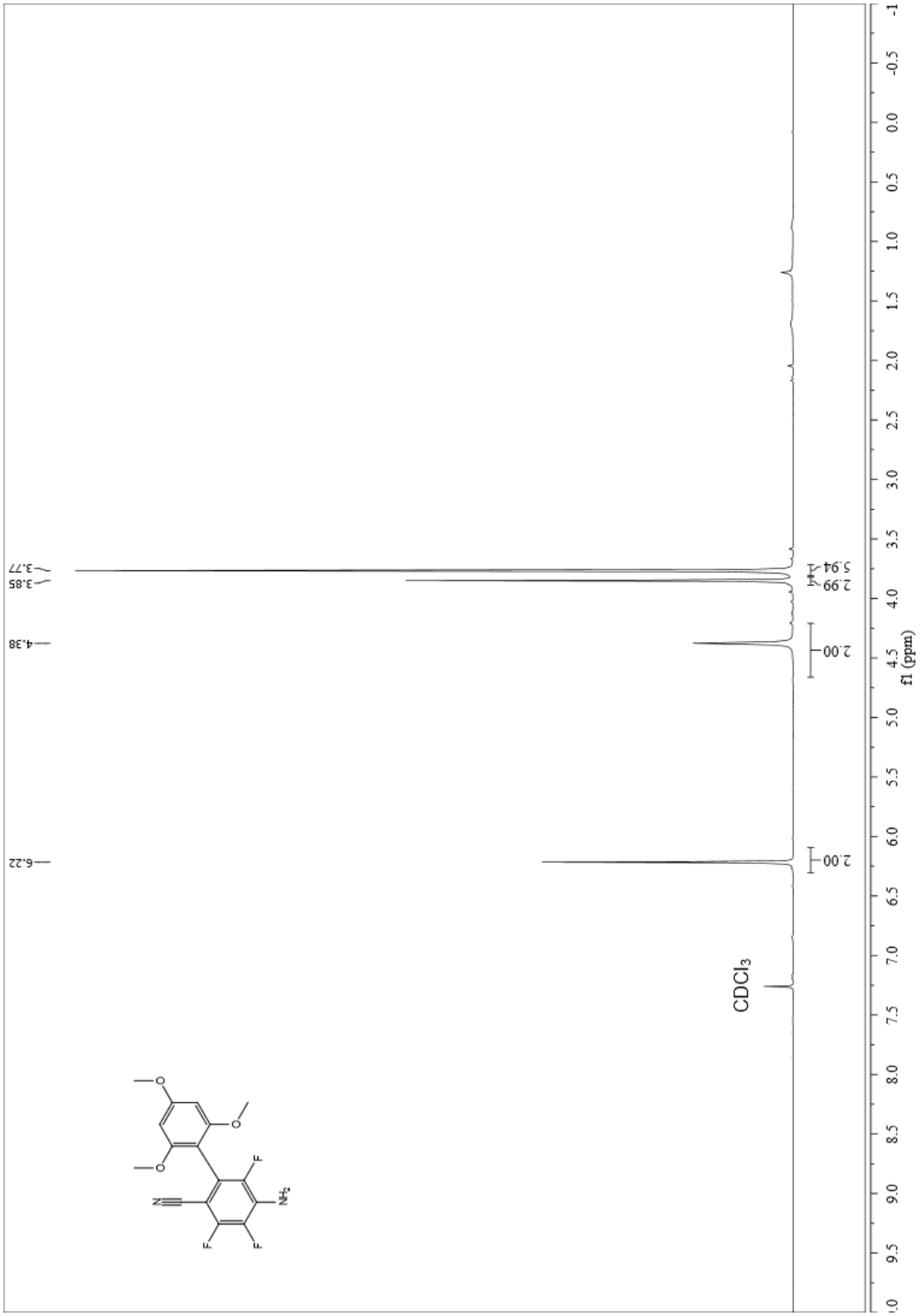




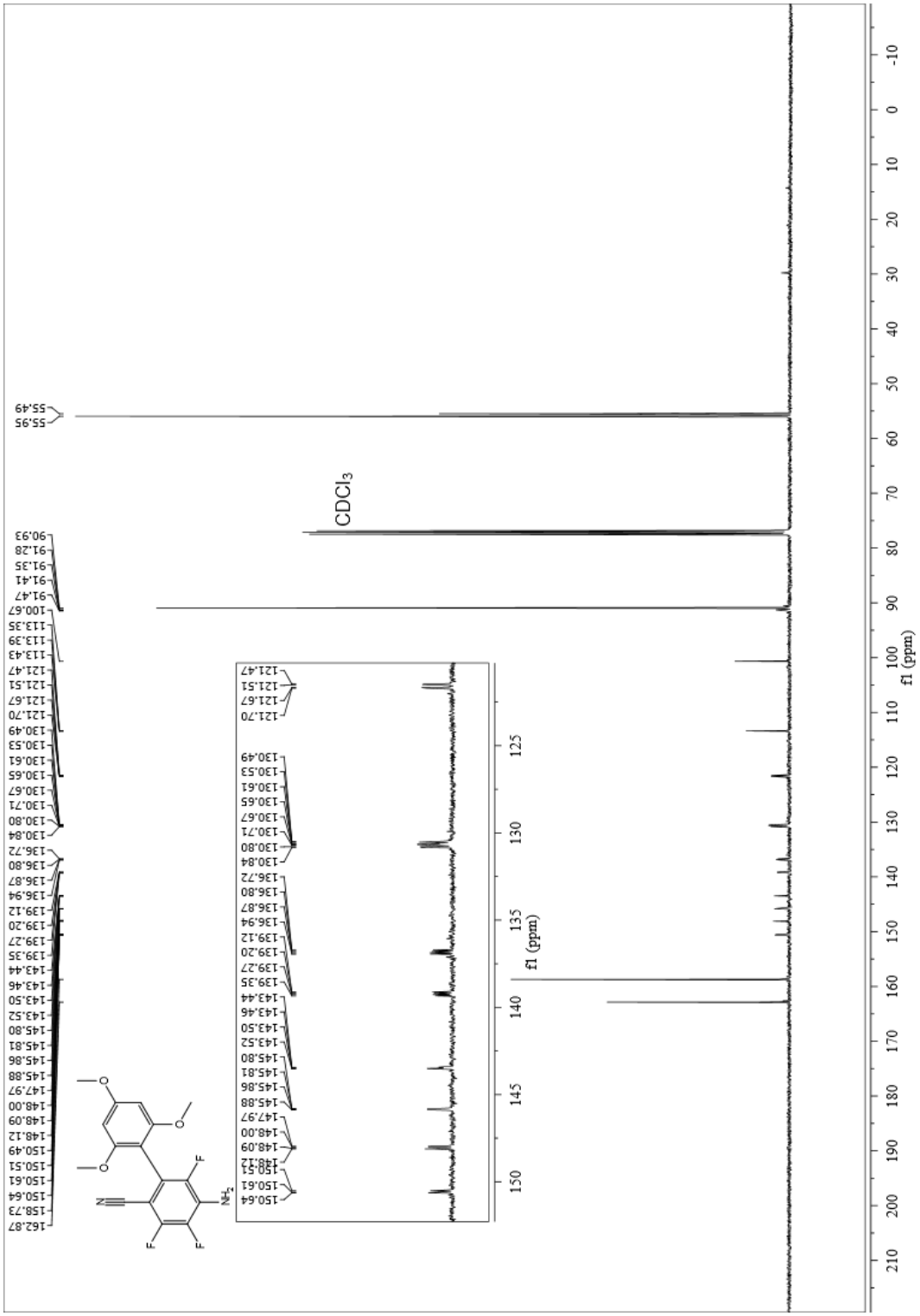
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6l (5-amino-3,4,6-trifluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-2-carbonitrile)



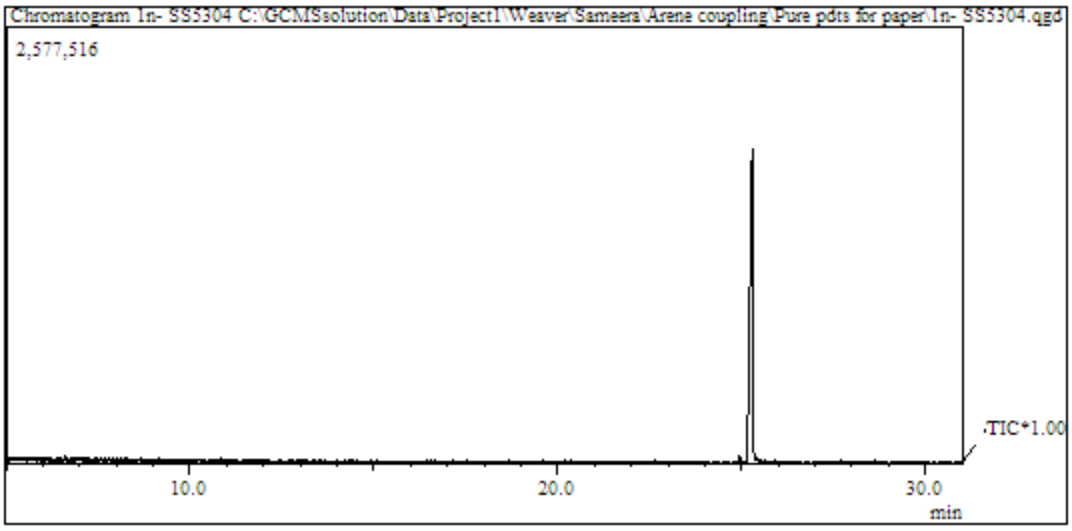
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6l (5-amino-3,4,6-trifluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-2-carbonitrile)

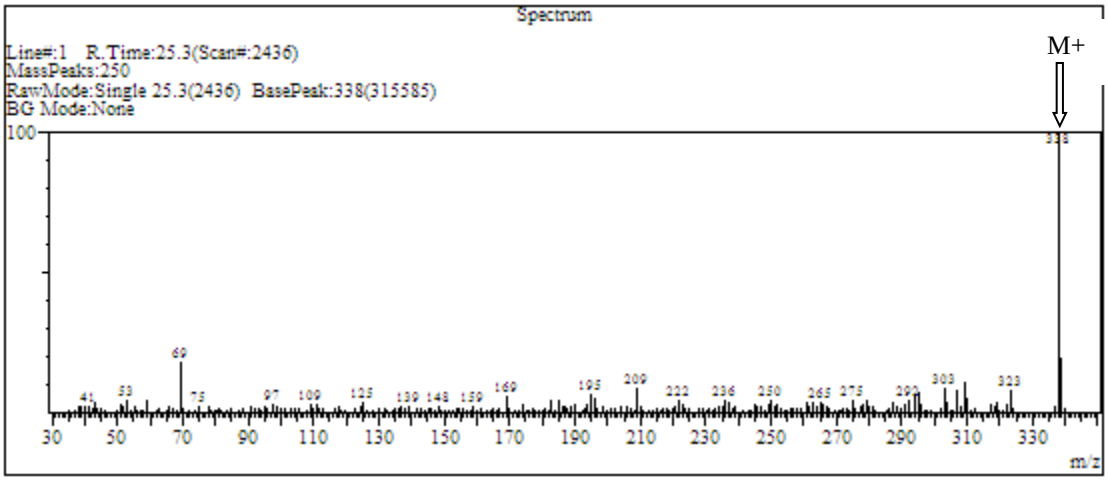


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6l (5-amino-3,4,6-trifluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-2-carbonitrile)

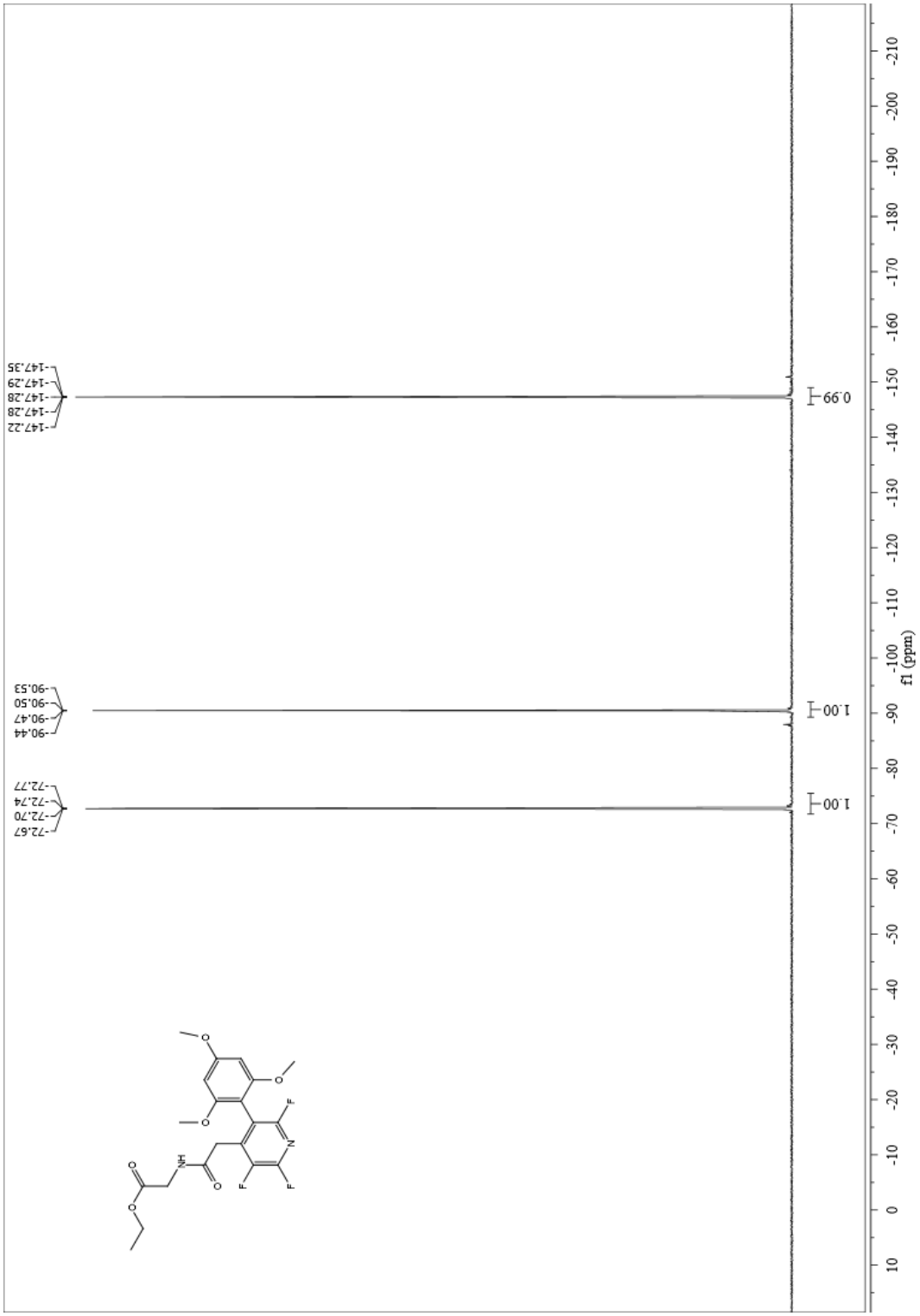


GC and MS of 3.6l (5-amino-3,4,6-trifluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-2-carbonitrile)

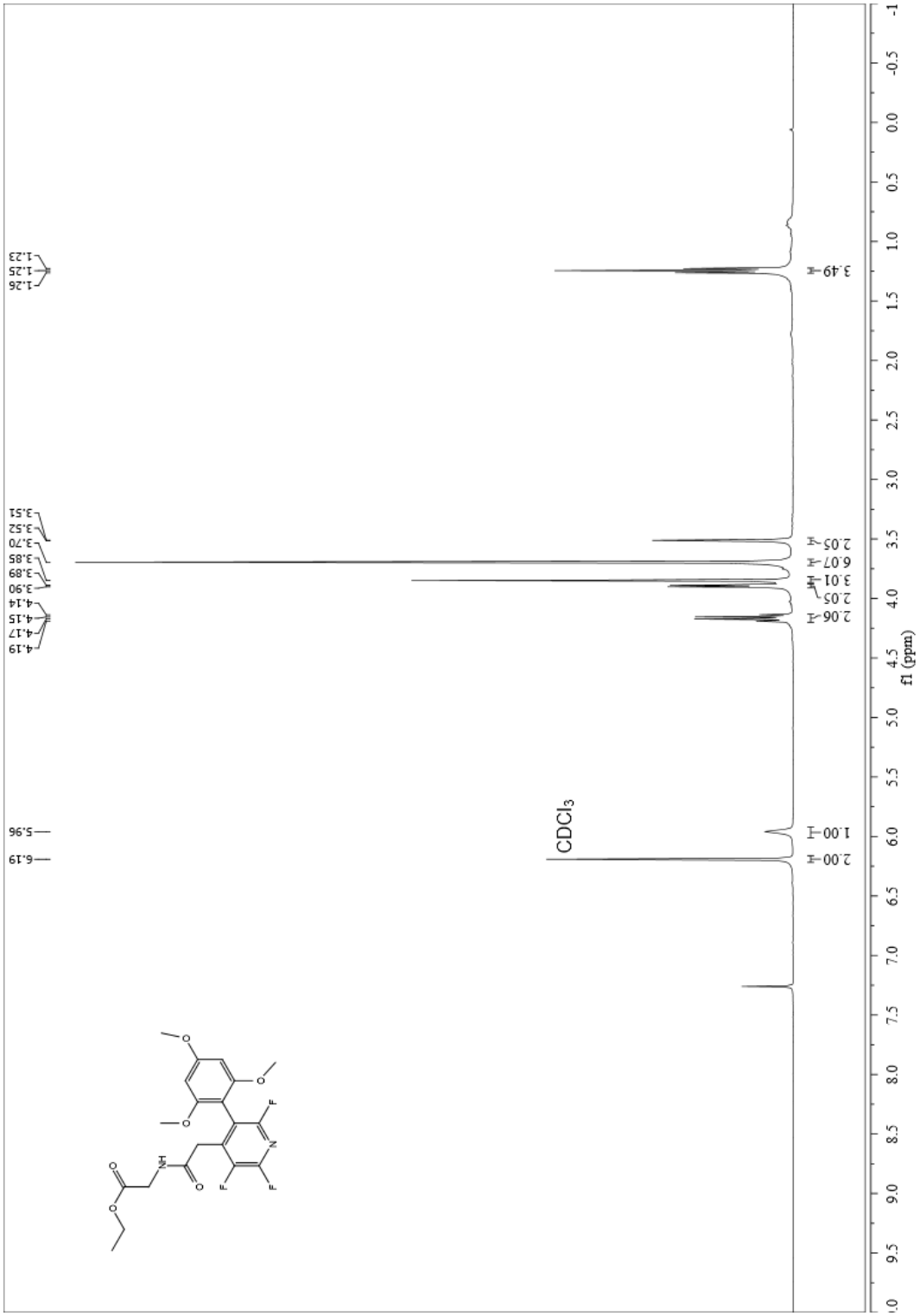




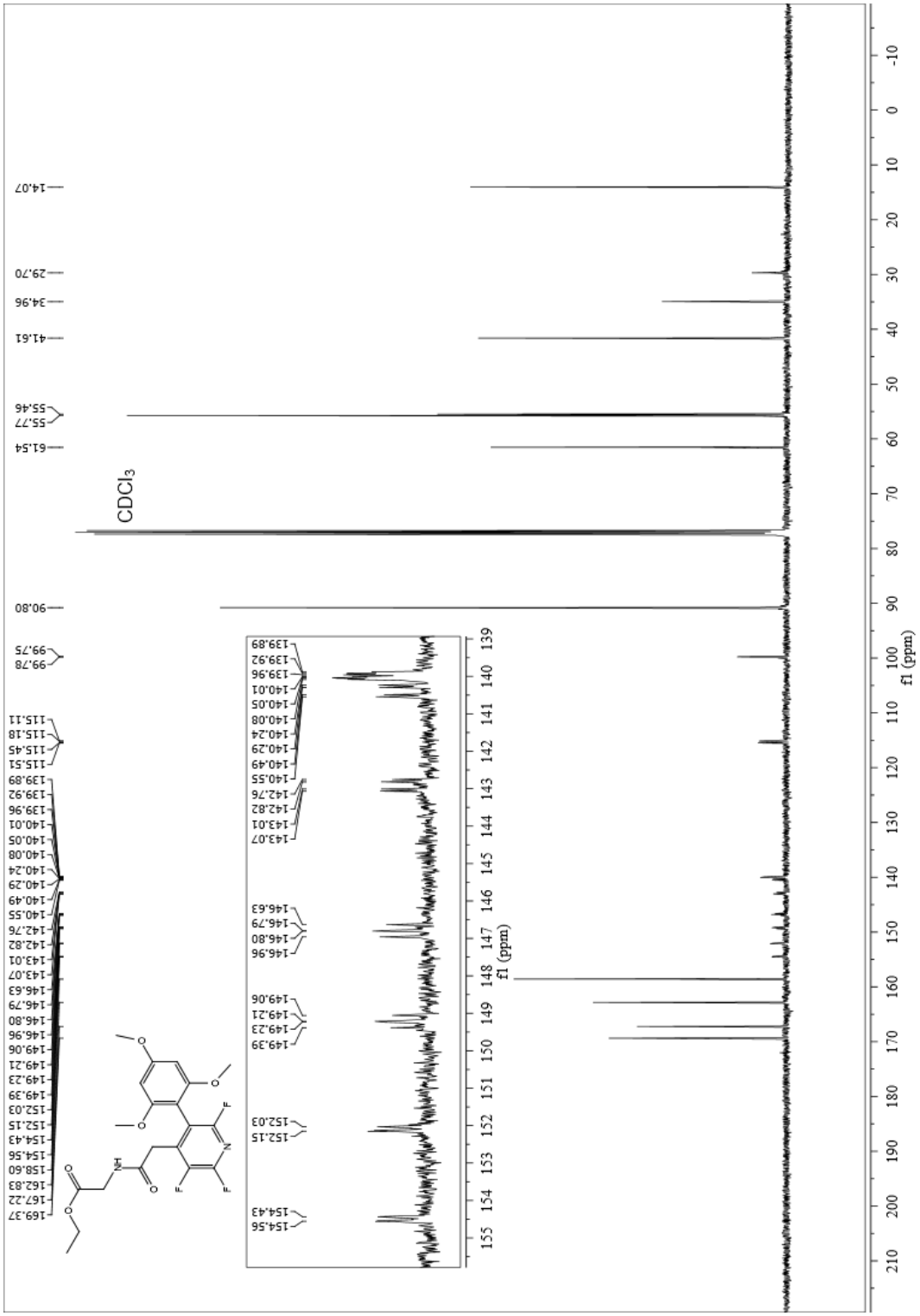
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6m (ethyl (2-(2,3,6-trifluoro-5-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)



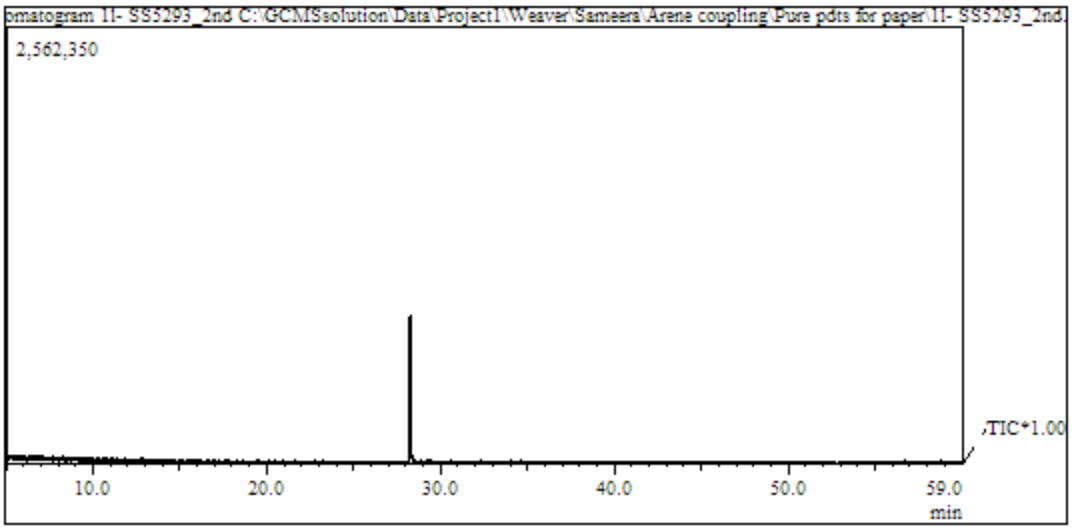
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6m (ethyl (2-(2,3,6-trifluoro-5-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)

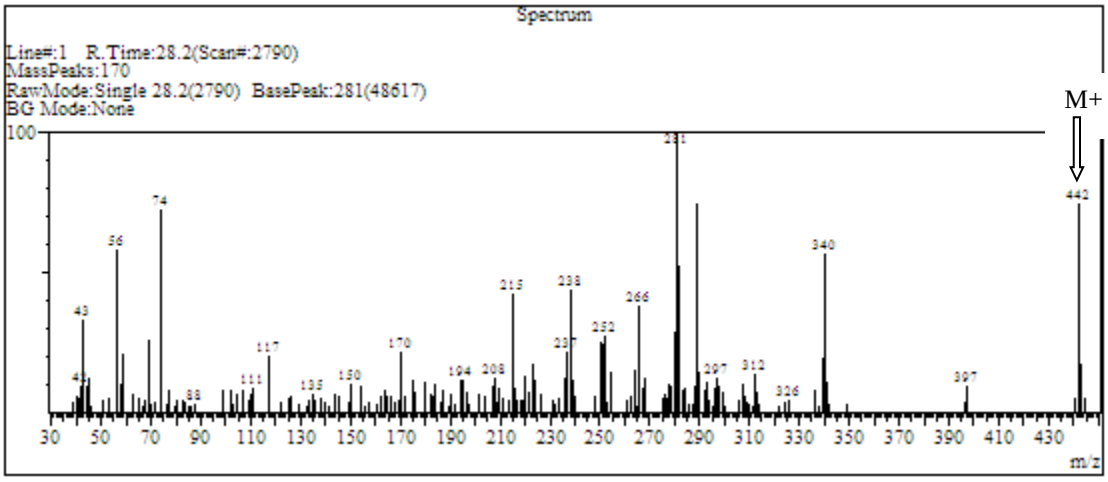


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6m (ethyl (2-(2,3,6-trifluoro-5-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)

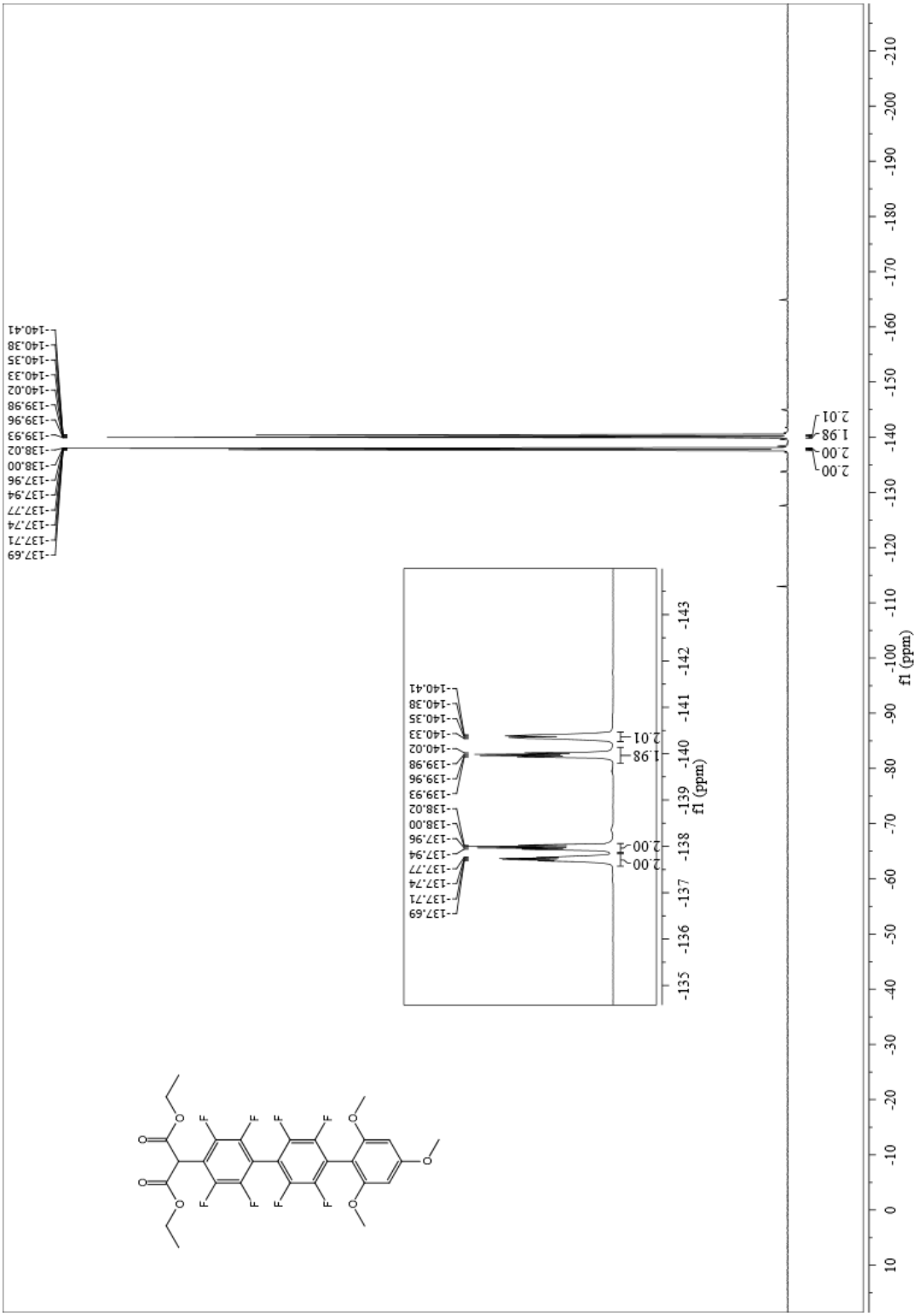


GC and MS of 3.6m (ethyl (2-(2,3,6-trifluoro-5-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)

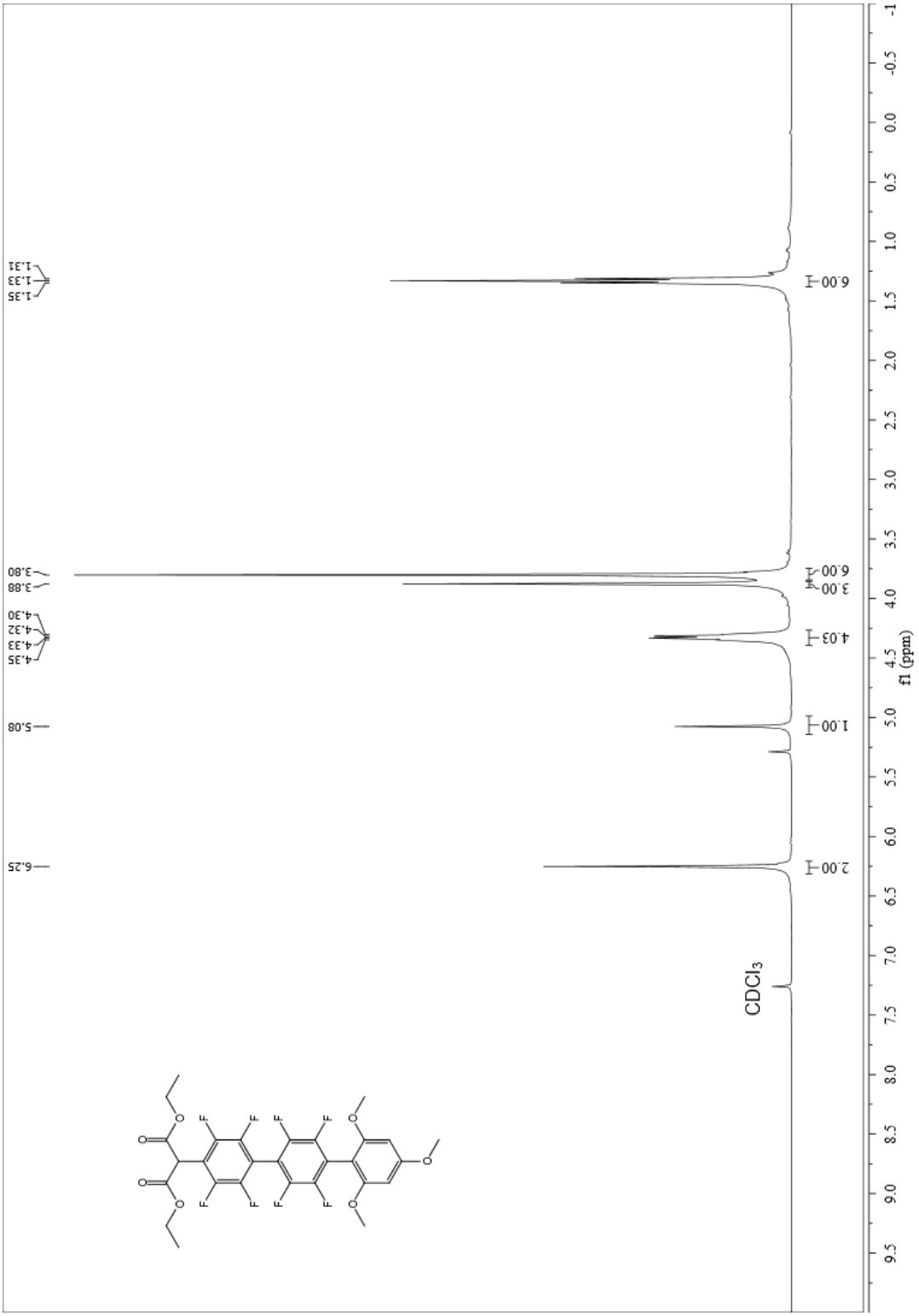




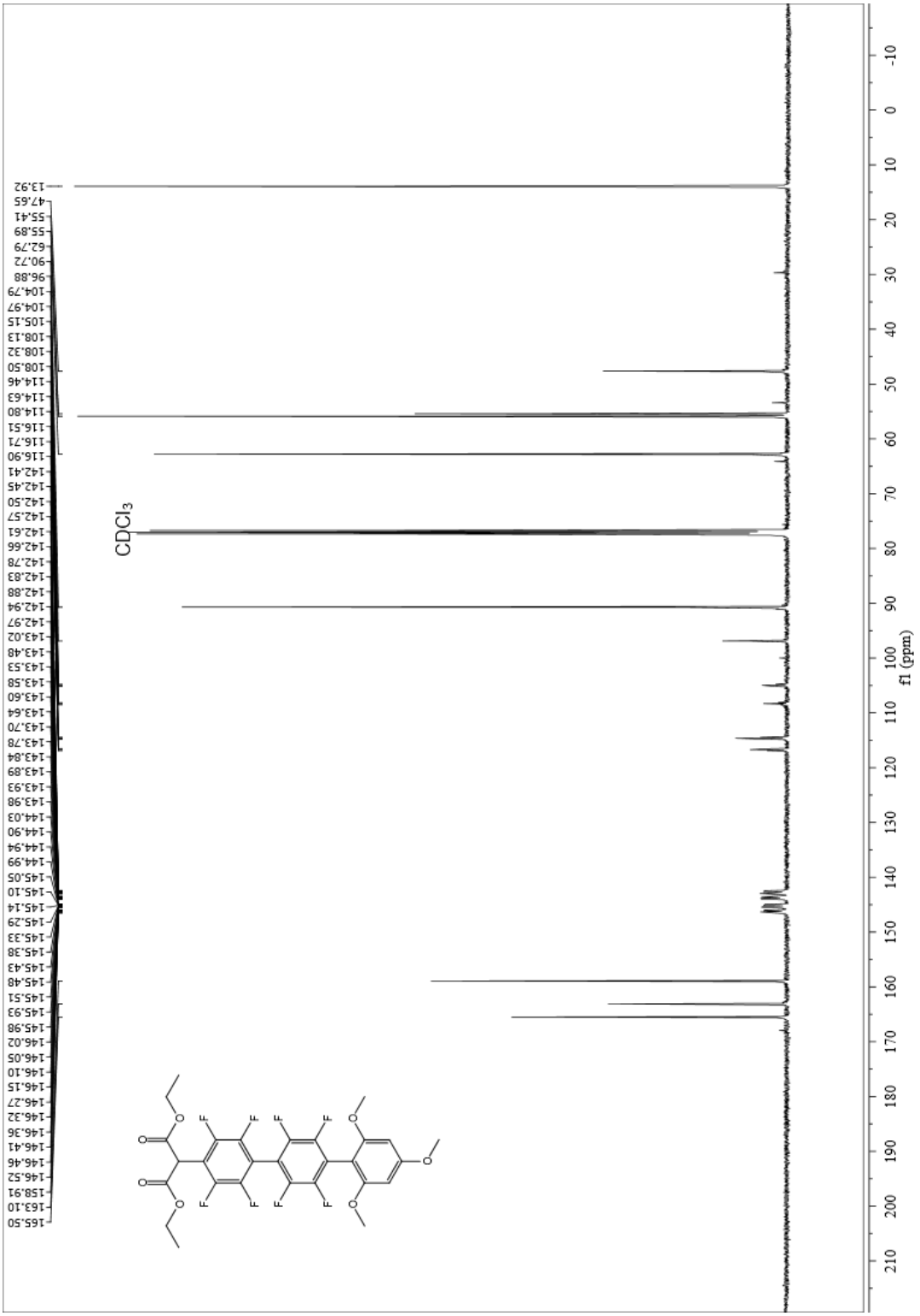
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6n (diethyl 2-(2,2',3,3',5,5',6,6'-octafluoro-2'',4'',6''-trimethoxy-[1,1':4',1''-terphenyl]-4-yl)malonate)



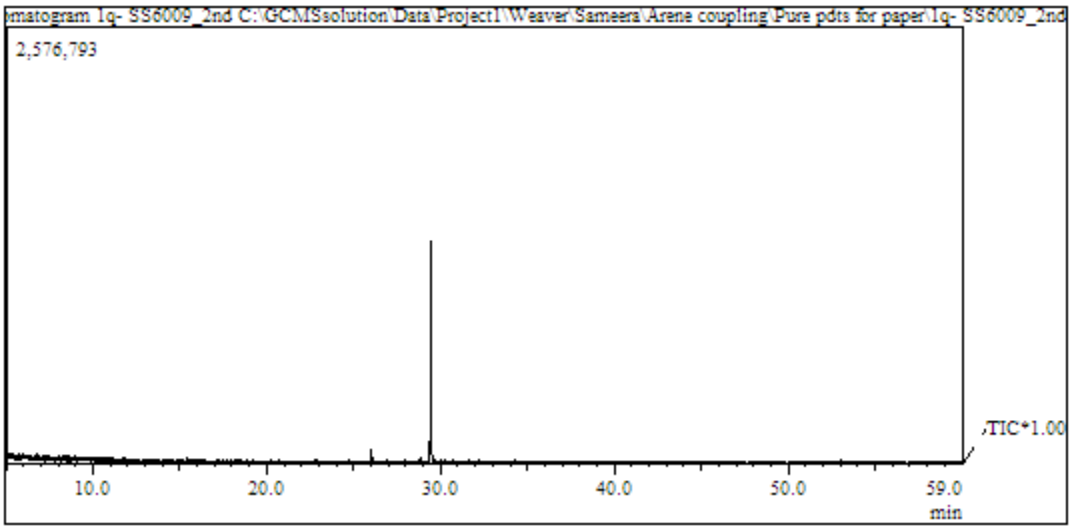
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6n (diethyl 2-(2,2',3,3',5,5',6,6'-octafluoro-2'',4'',6''-trimethoxy-[1,1':4',1''-terphenyl]-4-yl)malonate)

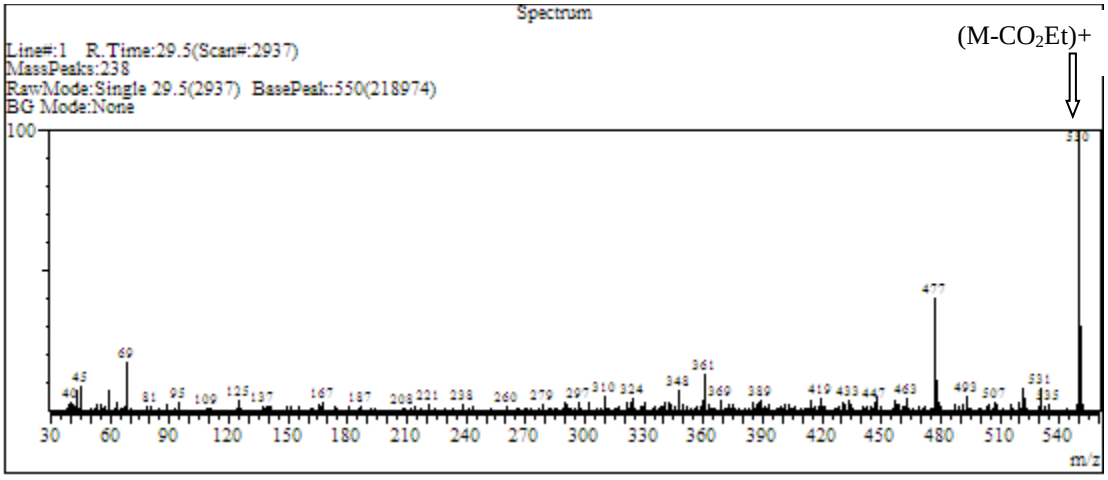


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6n (diethyl 2-(2,2',3,3',5,5',6,6'-octafluoro-2'',4'',6''-trimethoxy-[1,1':4',1''-terphenyl]-4-yl)malonate)

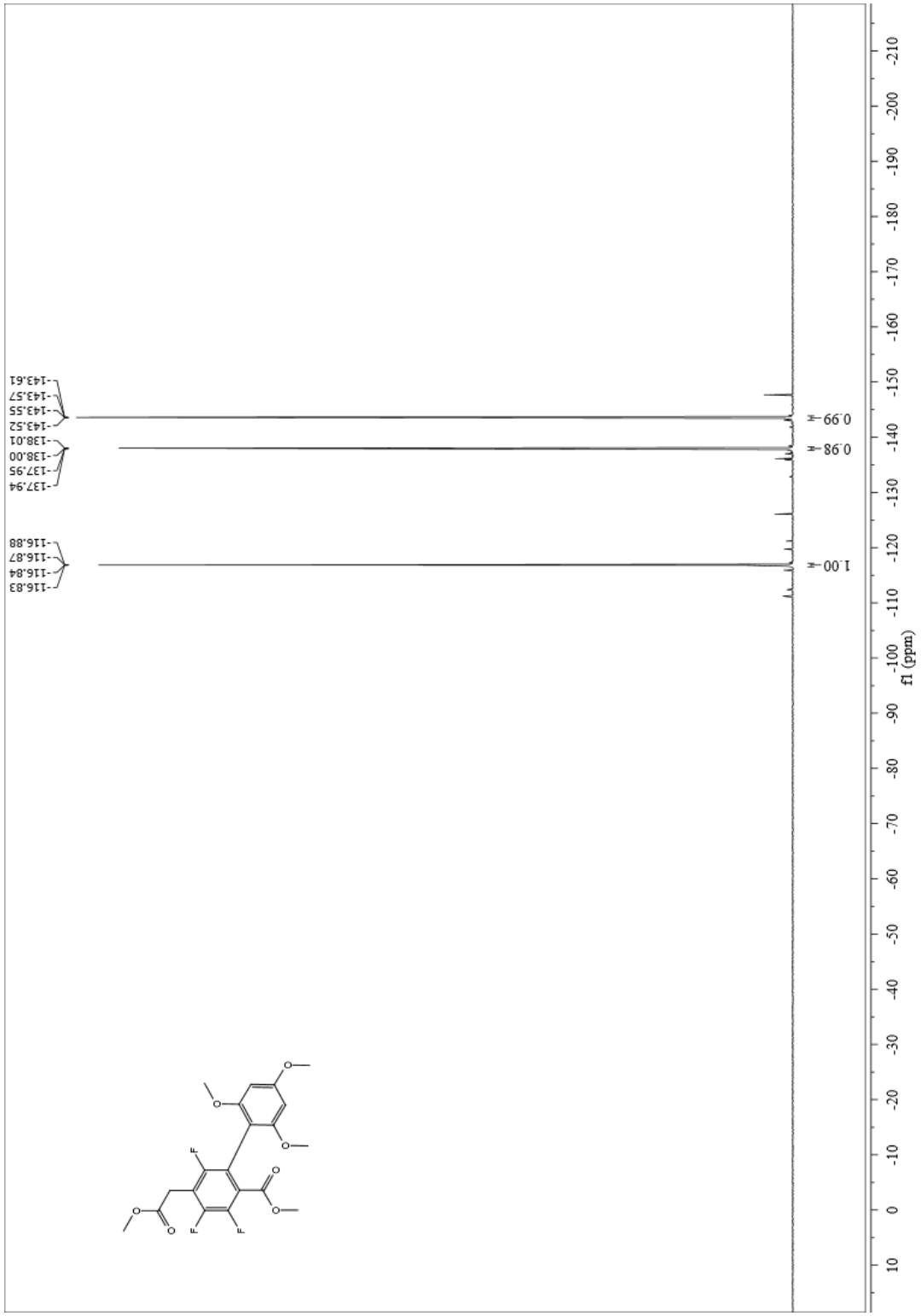


GC and MS of 3.6n (diethyl 2-(2,2',3,3',5,5',6,6'-octafluoro-2'',4'',6''-trimethoxy-[1,1':4',1''-terphenyl]-4-yl)malonate)

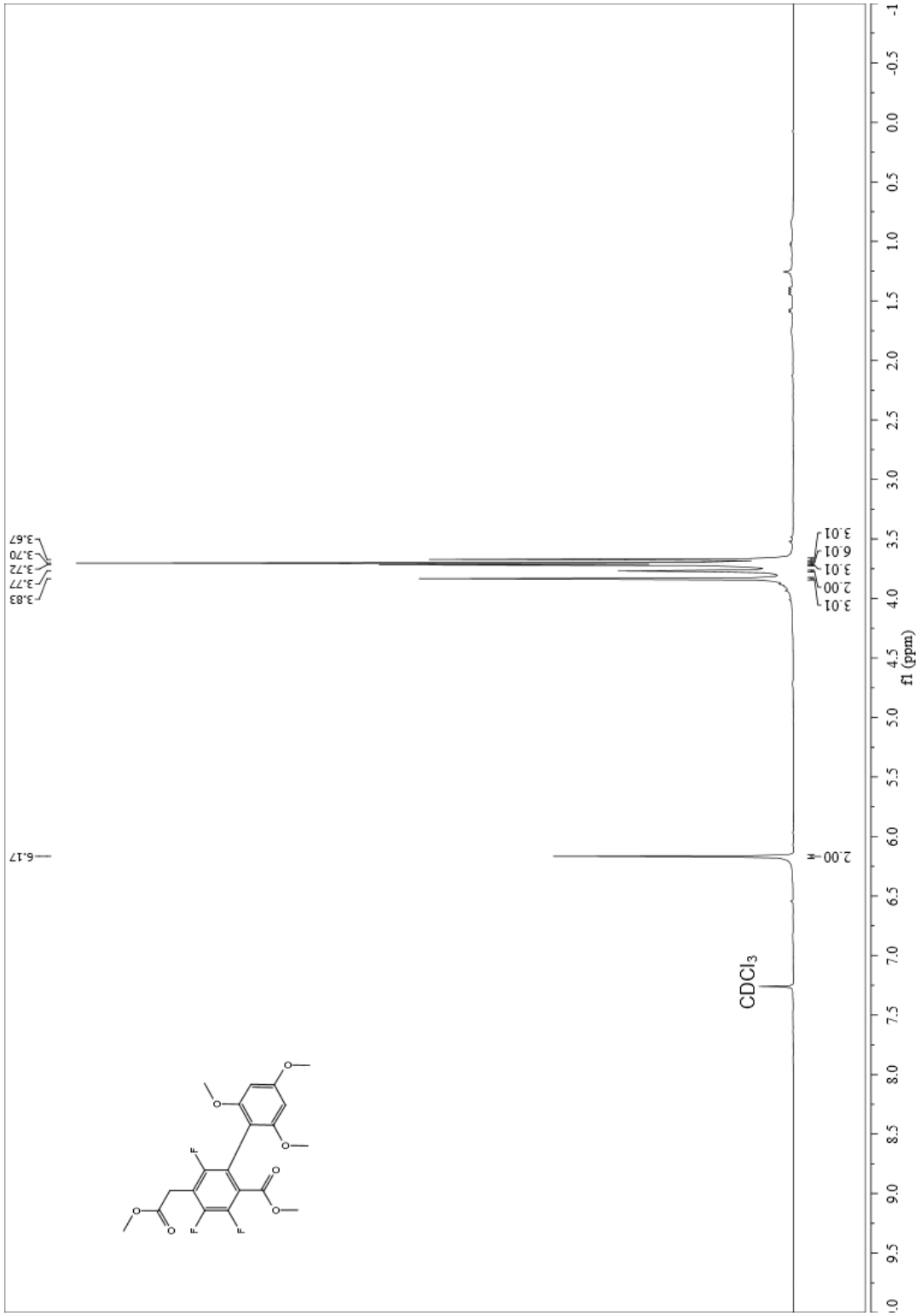




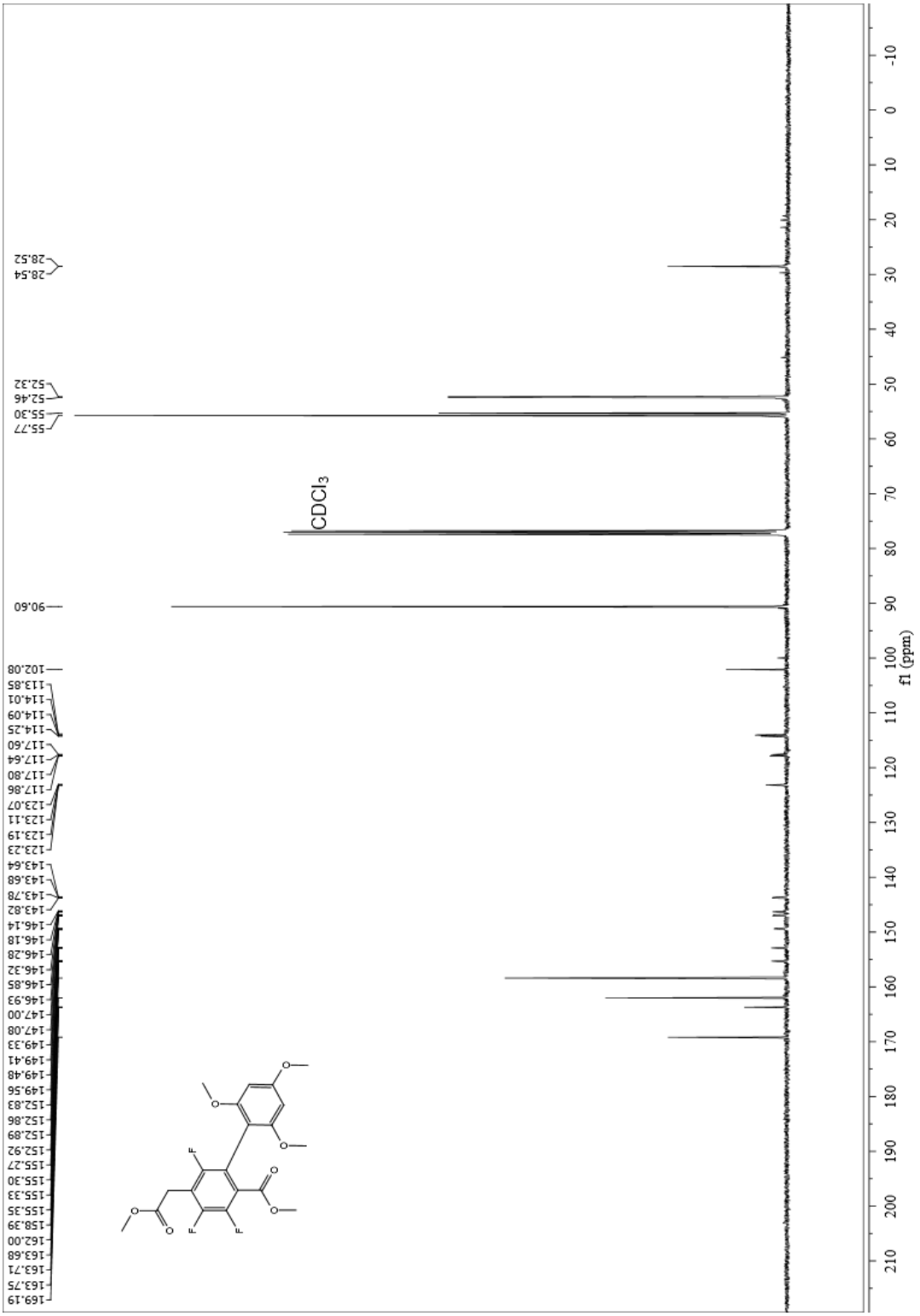
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6o (methyl 3,4,6-trifluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)



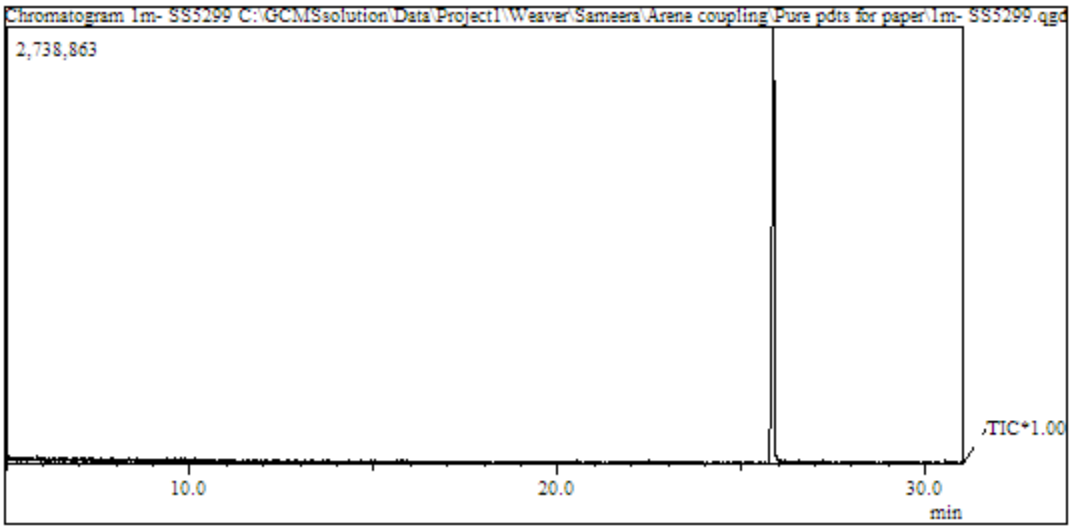
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6o (methyl 3,4,6-trifluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)

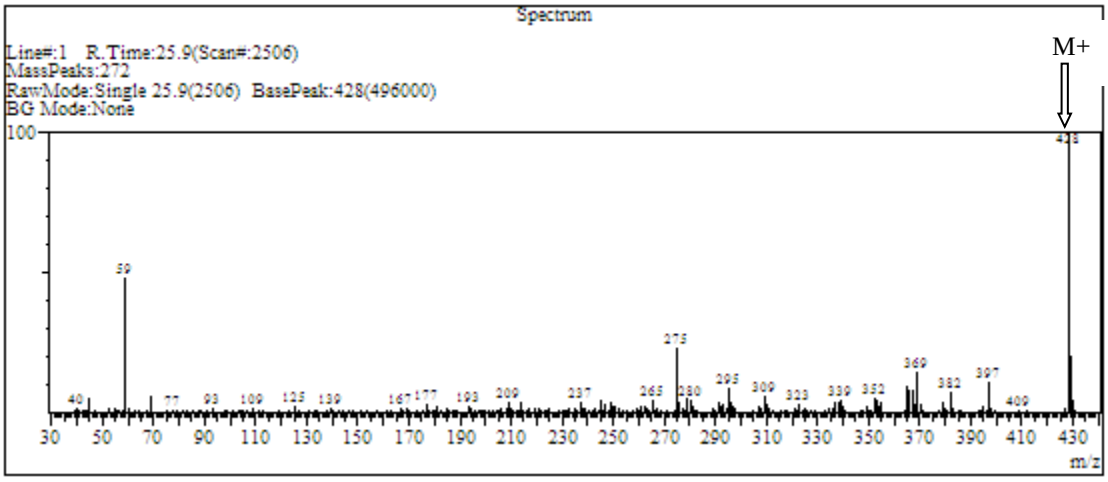


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6o (methyl 3,4,6-trifluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)

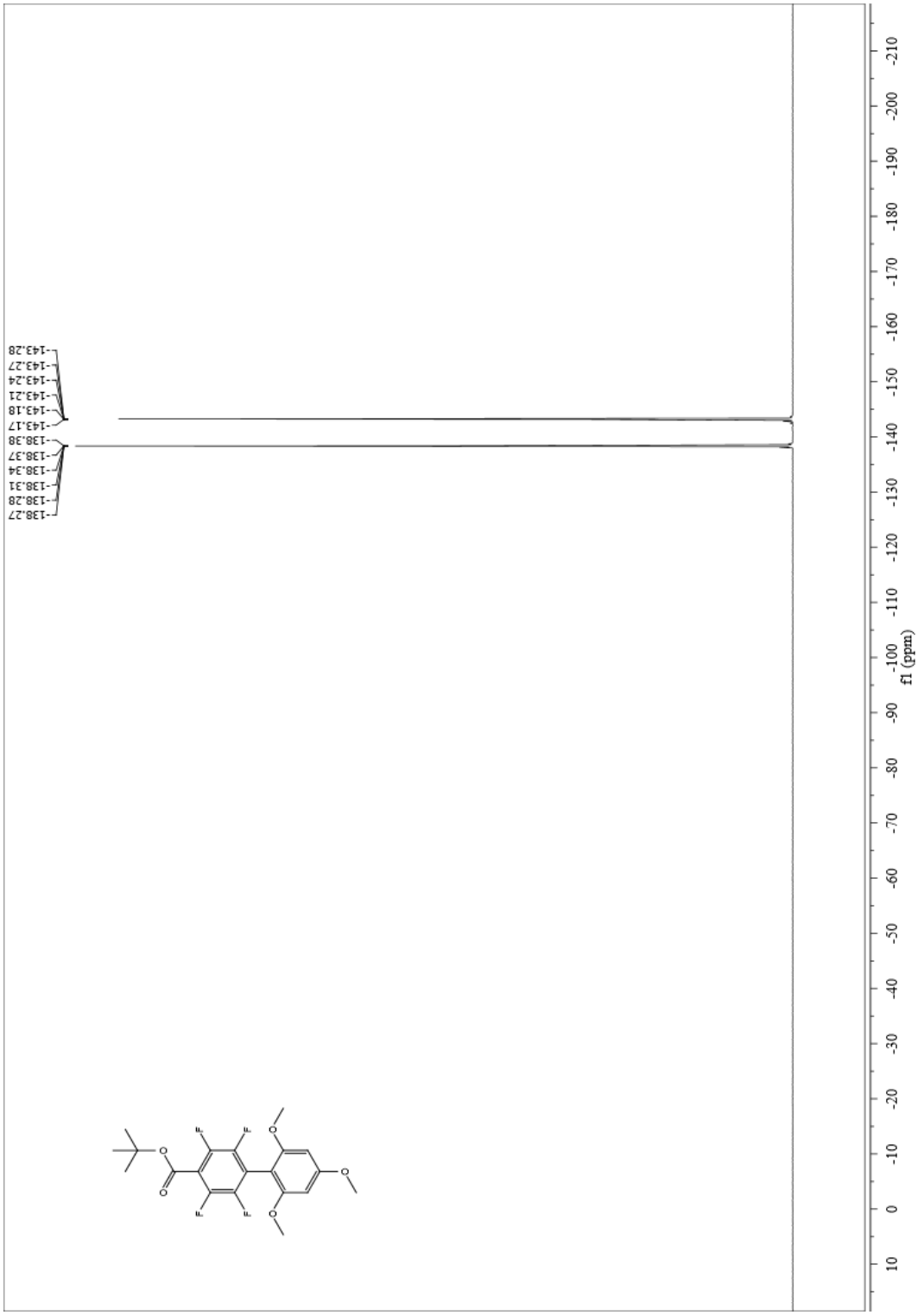


GC and MS of 3.6o (methyl 3,4,6-trifluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)

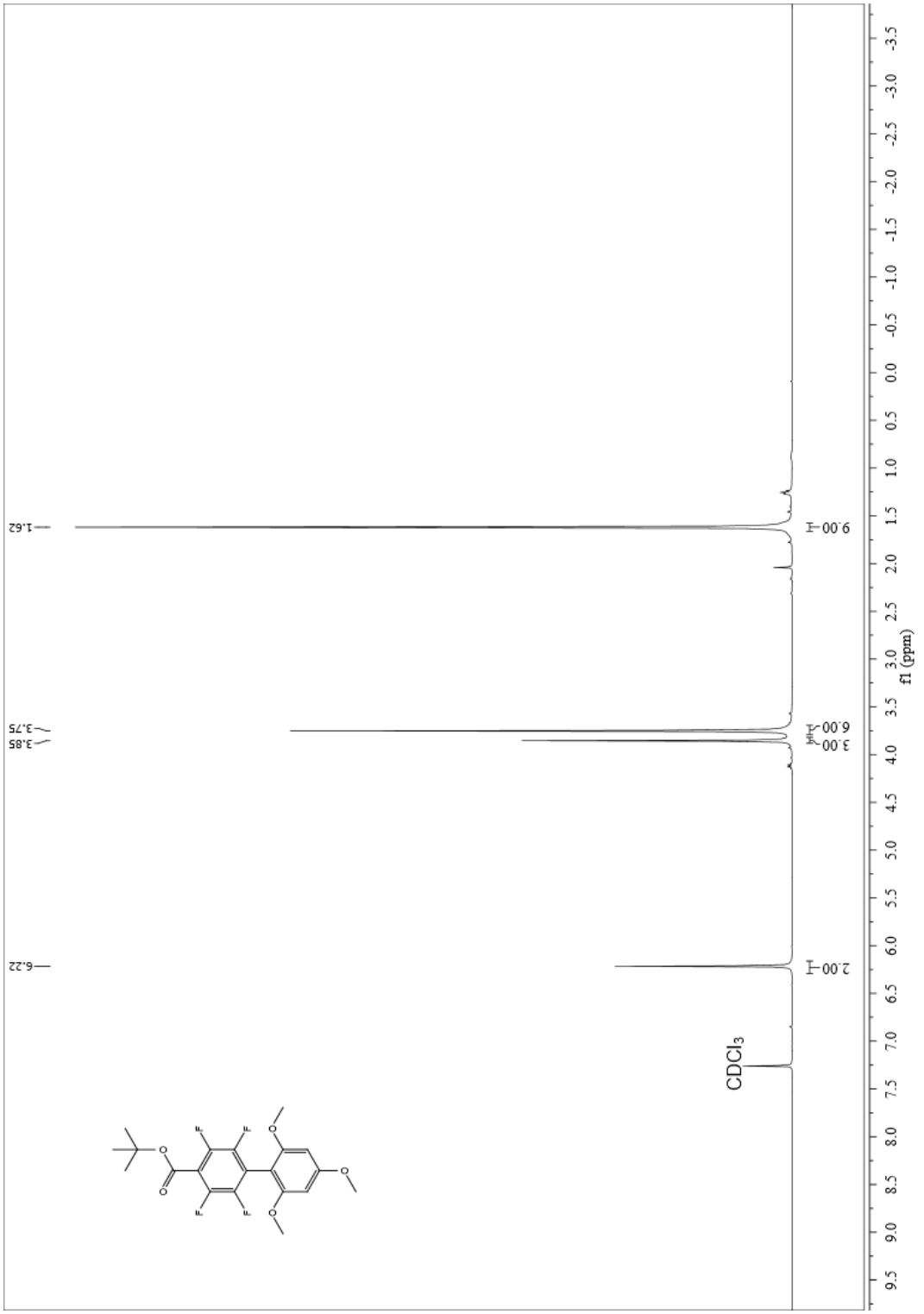




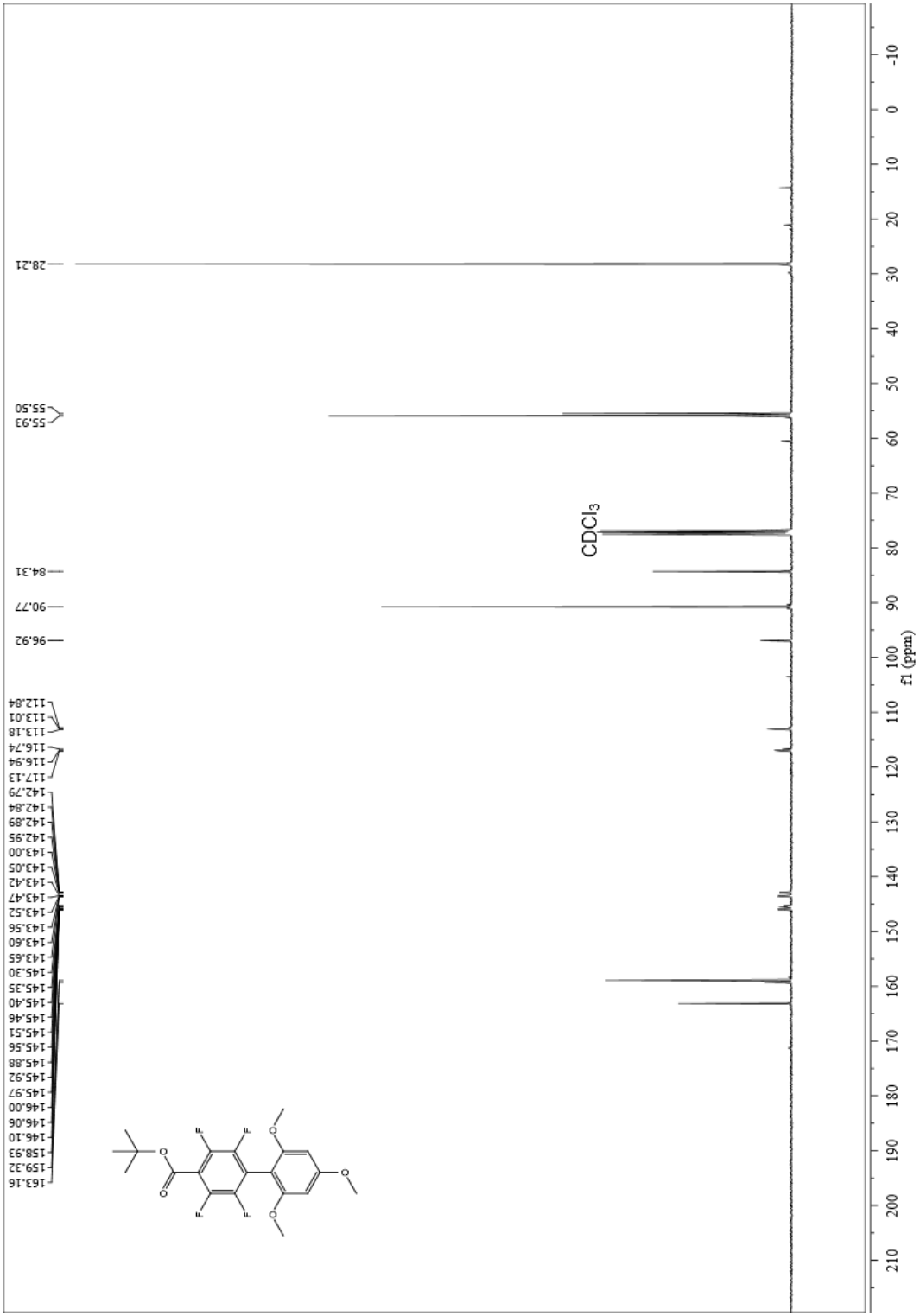
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6p (tert-butyl 2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carboxylate)



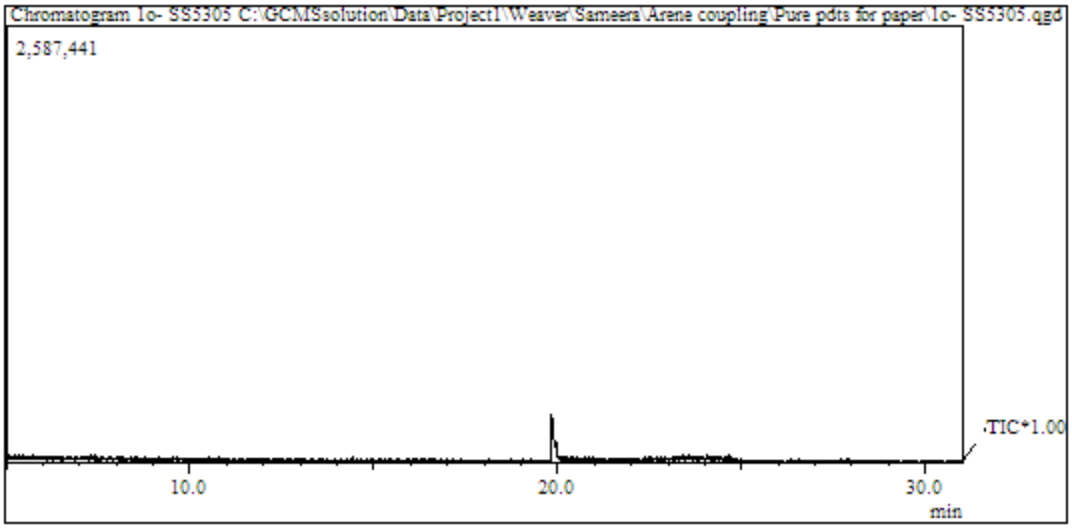
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6p (tert-butyl 2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carboxylate)

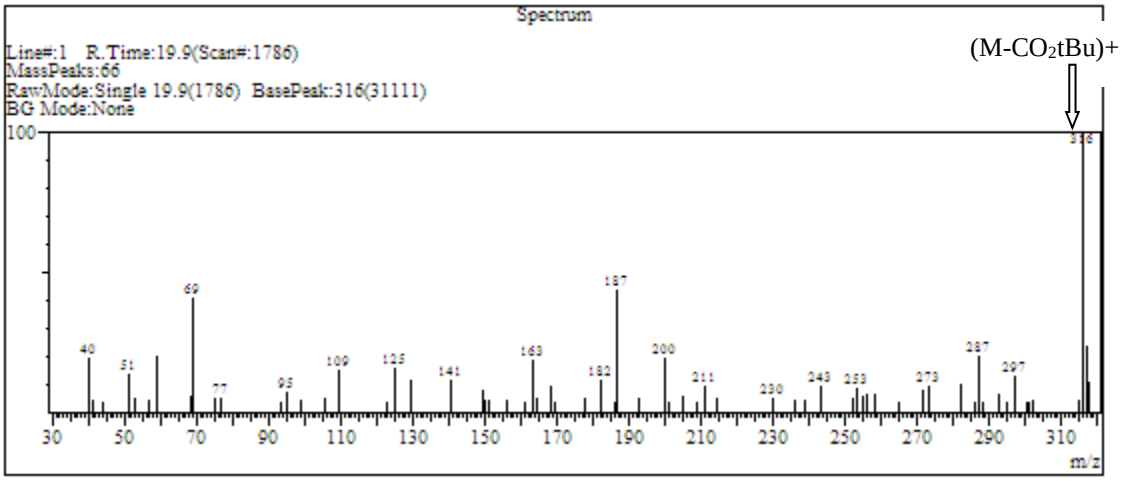


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6p (tert-butyl 2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carboxylate)

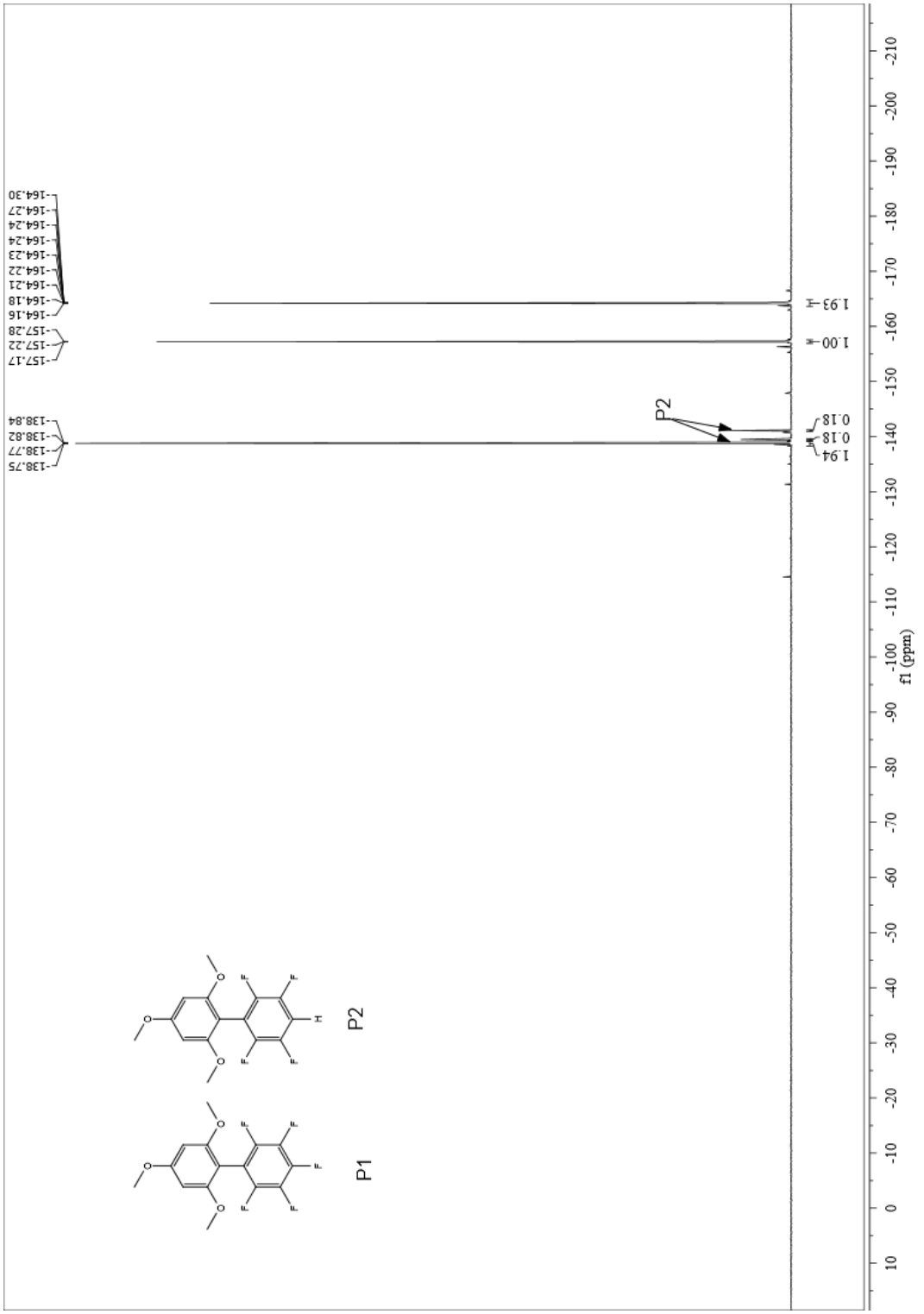


GC and MS of 3.6p (tert-butyl 2,3,5,6-tetrafluoro-2',4',6'-trimethoxy-[1,1'-biphenyl]-4-carboxylate)

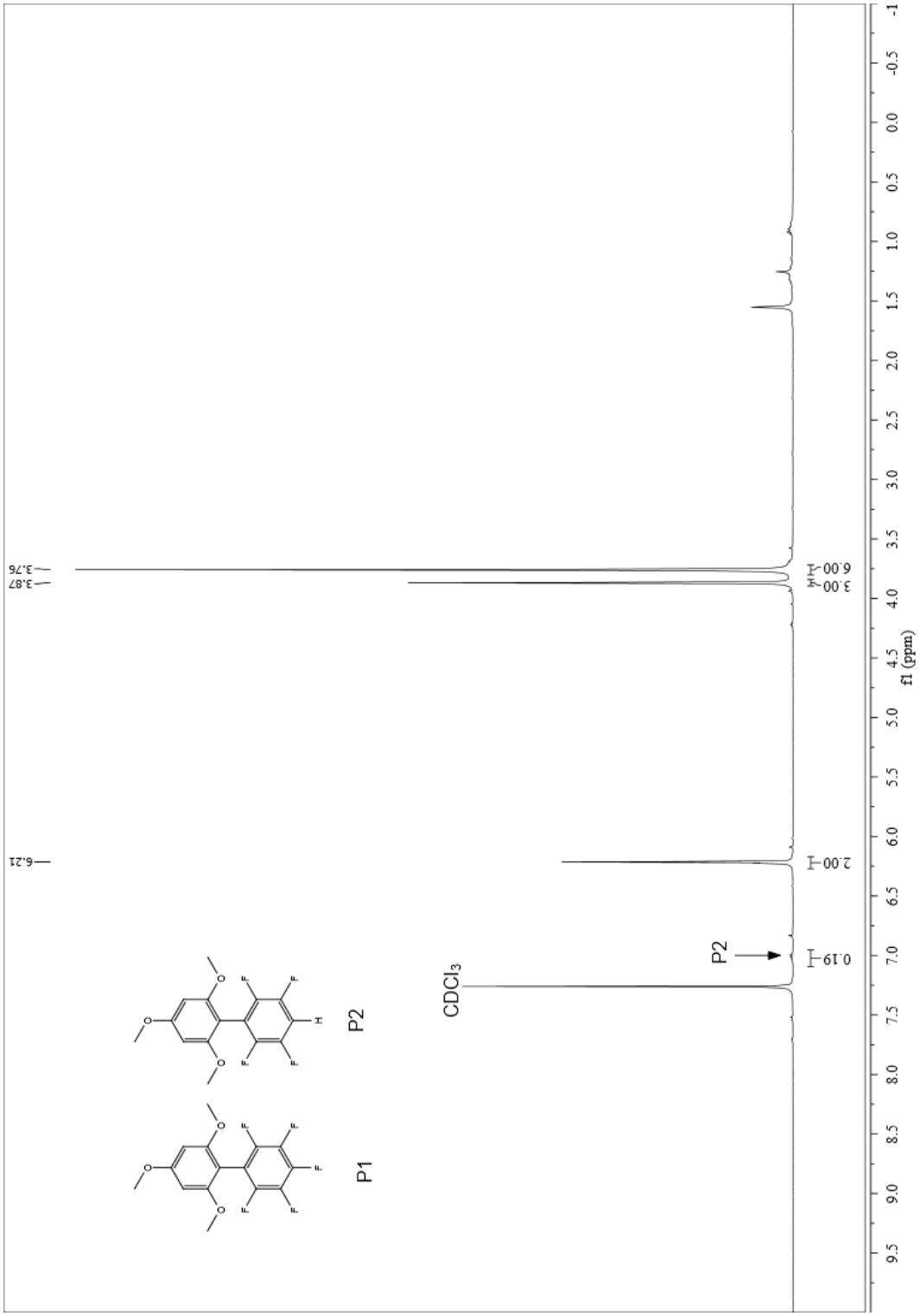




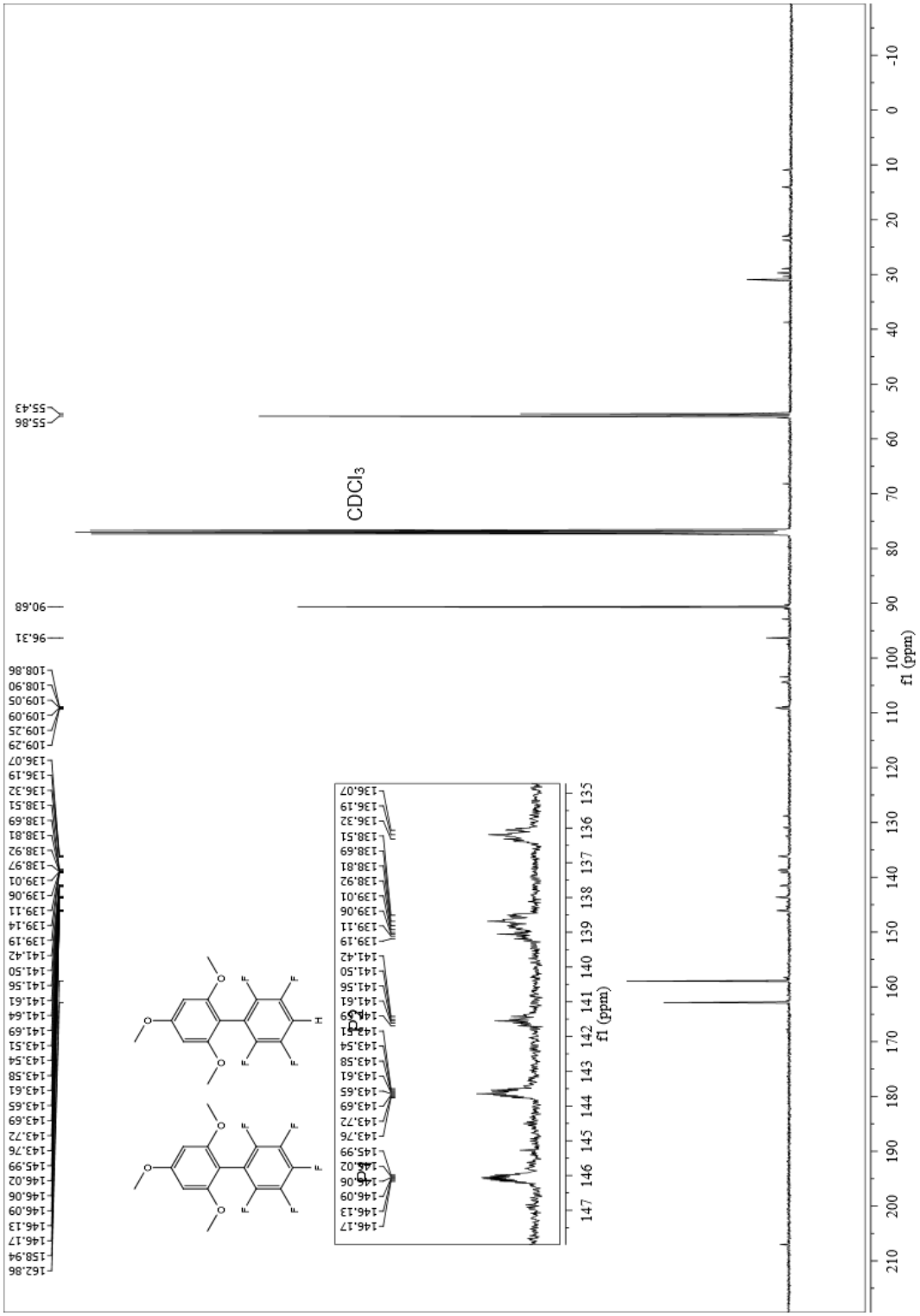
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6q (2,3,4,5,6-pentafluoro-2',4',6'-trimethoxy-1,1'-biphenyl)



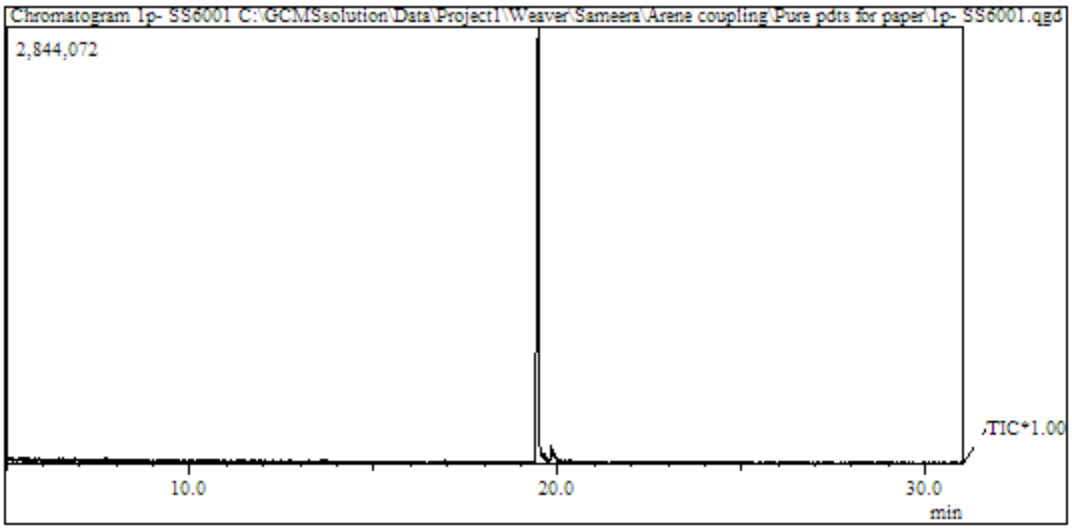
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6q (2,3,4,5,6-pentafluoro-2',4',6'-trimethoxy-1,1'-biphenyl)

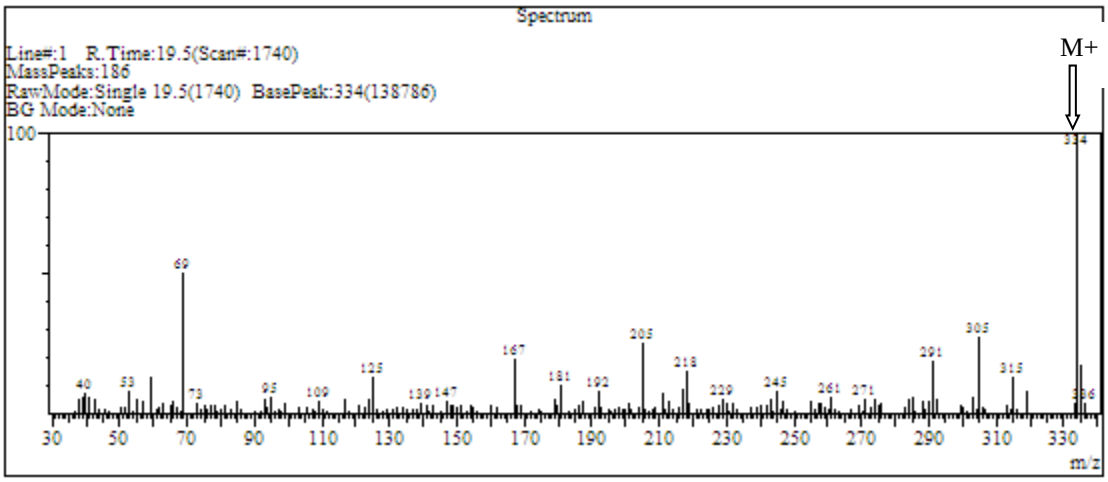


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.6q (2,3,4,5,6-pentafluoro-2',4',6'-trimethoxy-1,1'-biphenyl)

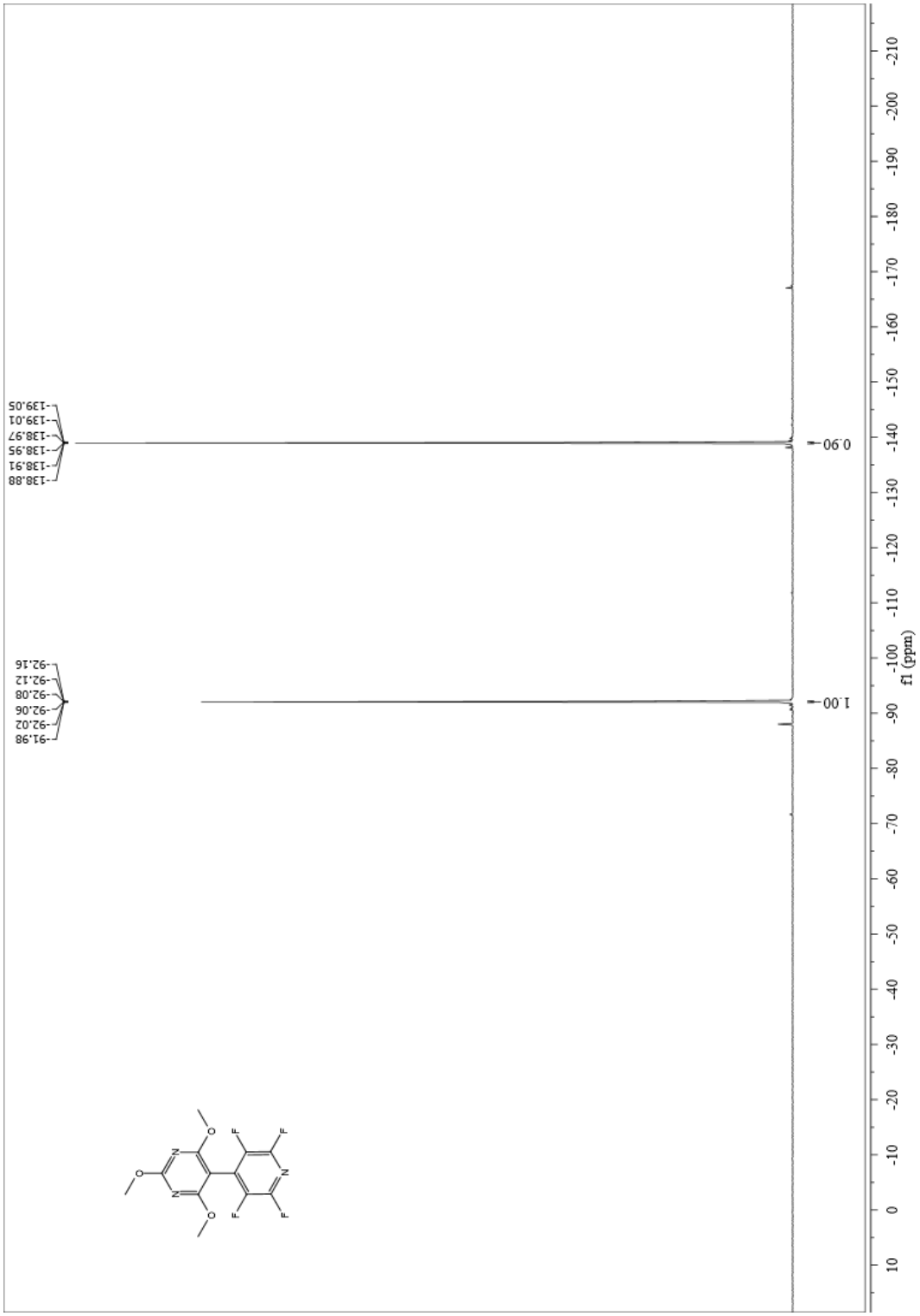


GC and MS of 3.6q (2,3,4,5,6-pentafluoro-2',4',6'-trimethoxy-1,1'-biphenyl)

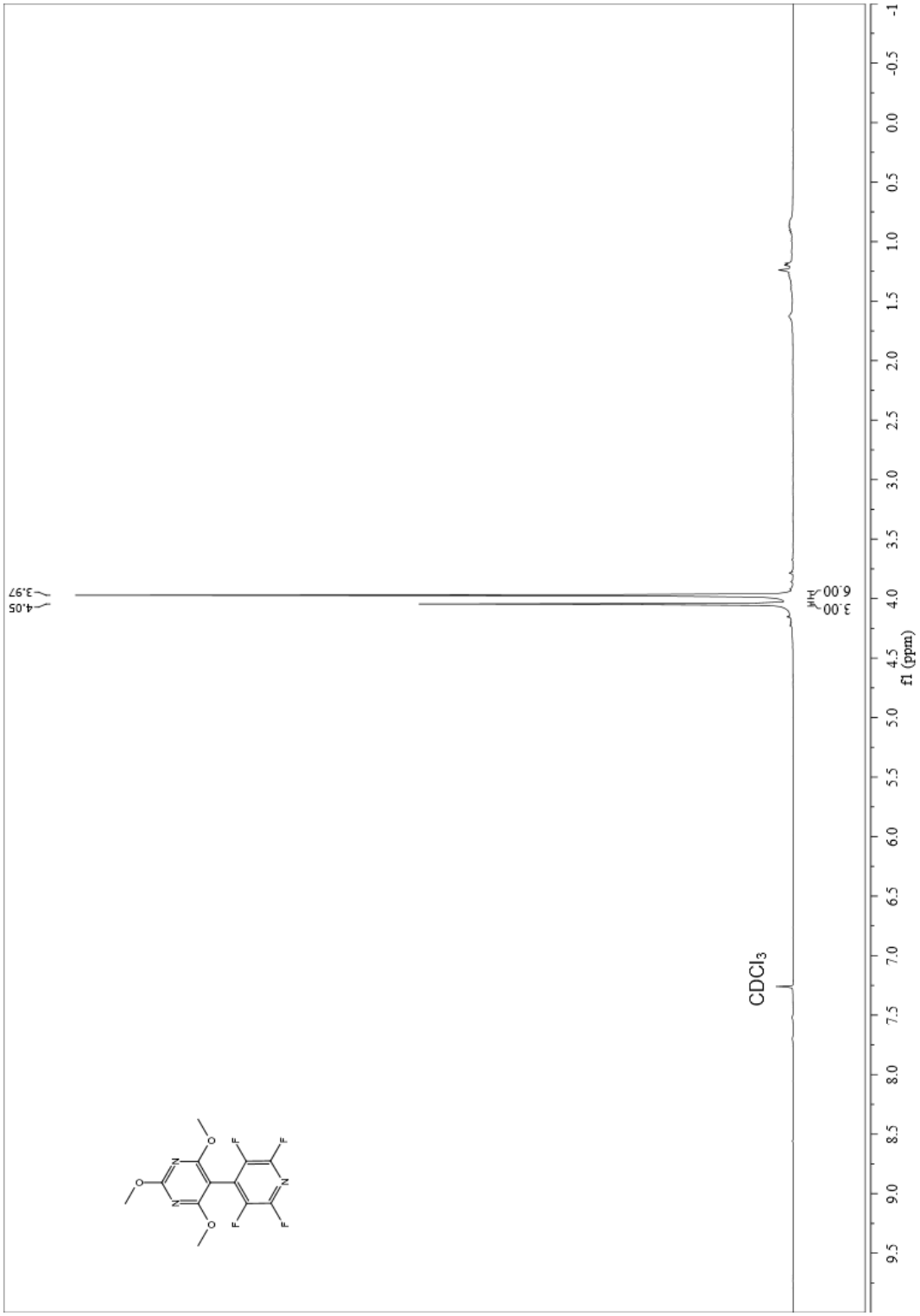




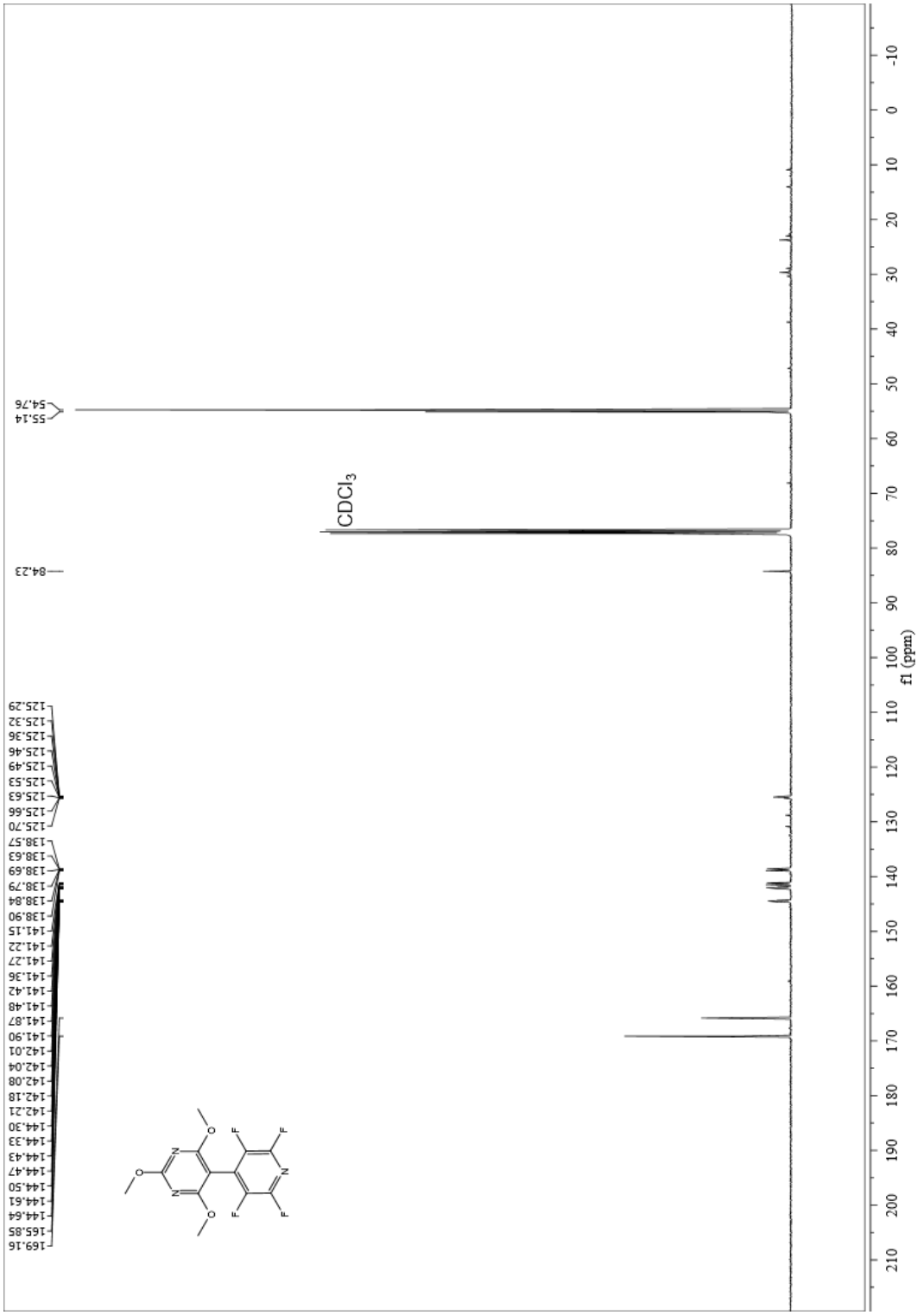
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9a (2,4,6-trimethoxy-5-(perfluoropyridin-4-yl)pyrimidine)



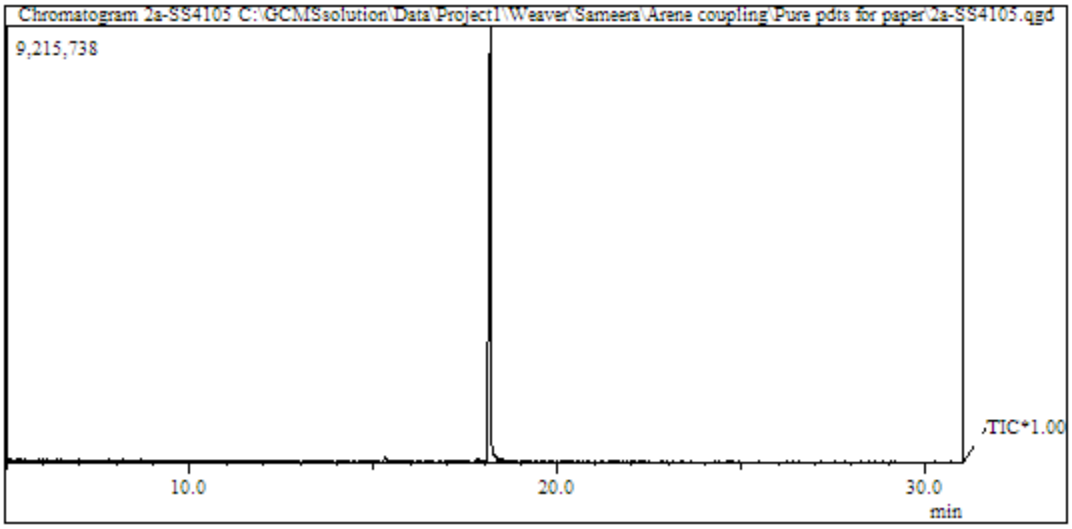
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9a (2,4,6-trimethoxy-5-(perfluoropyridin-4-yl)pyrimidine)

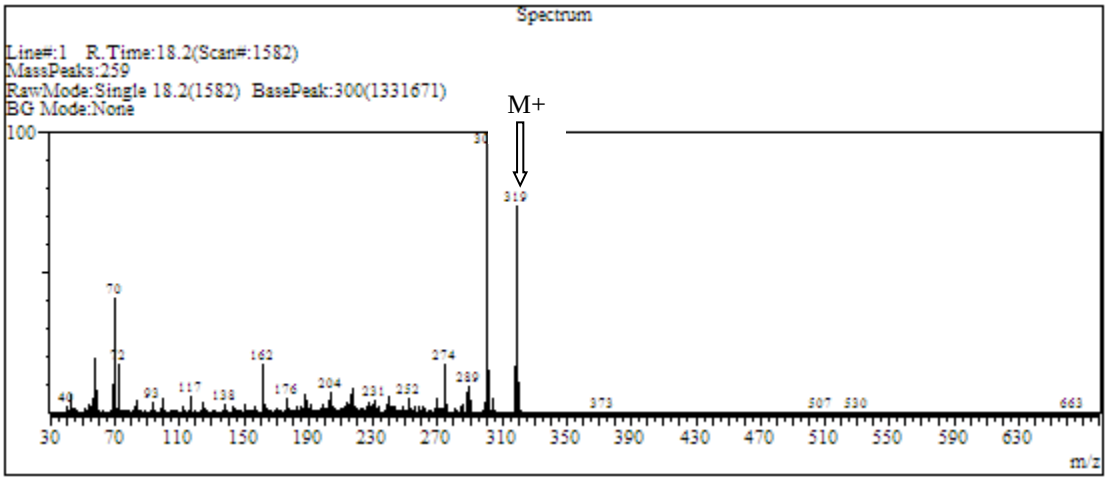


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9a (2,4,6-trimethoxy-5-(perfluoropyridin-4-yl)pyrimidine)

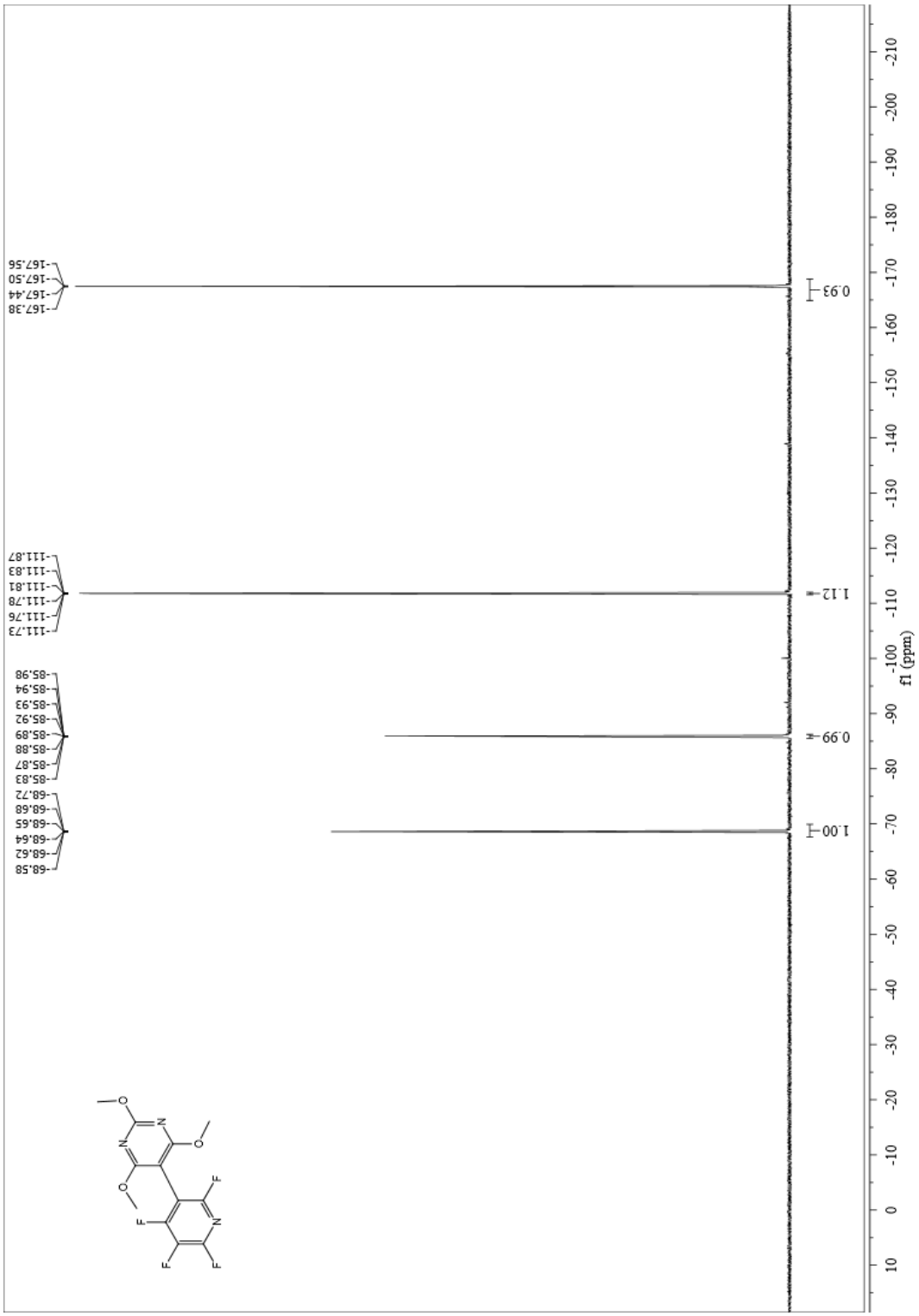


GC and MS of 3.9a (2,4,6-trimethoxy-5-(perfluoropyridin-4-yl)pyrimidine)

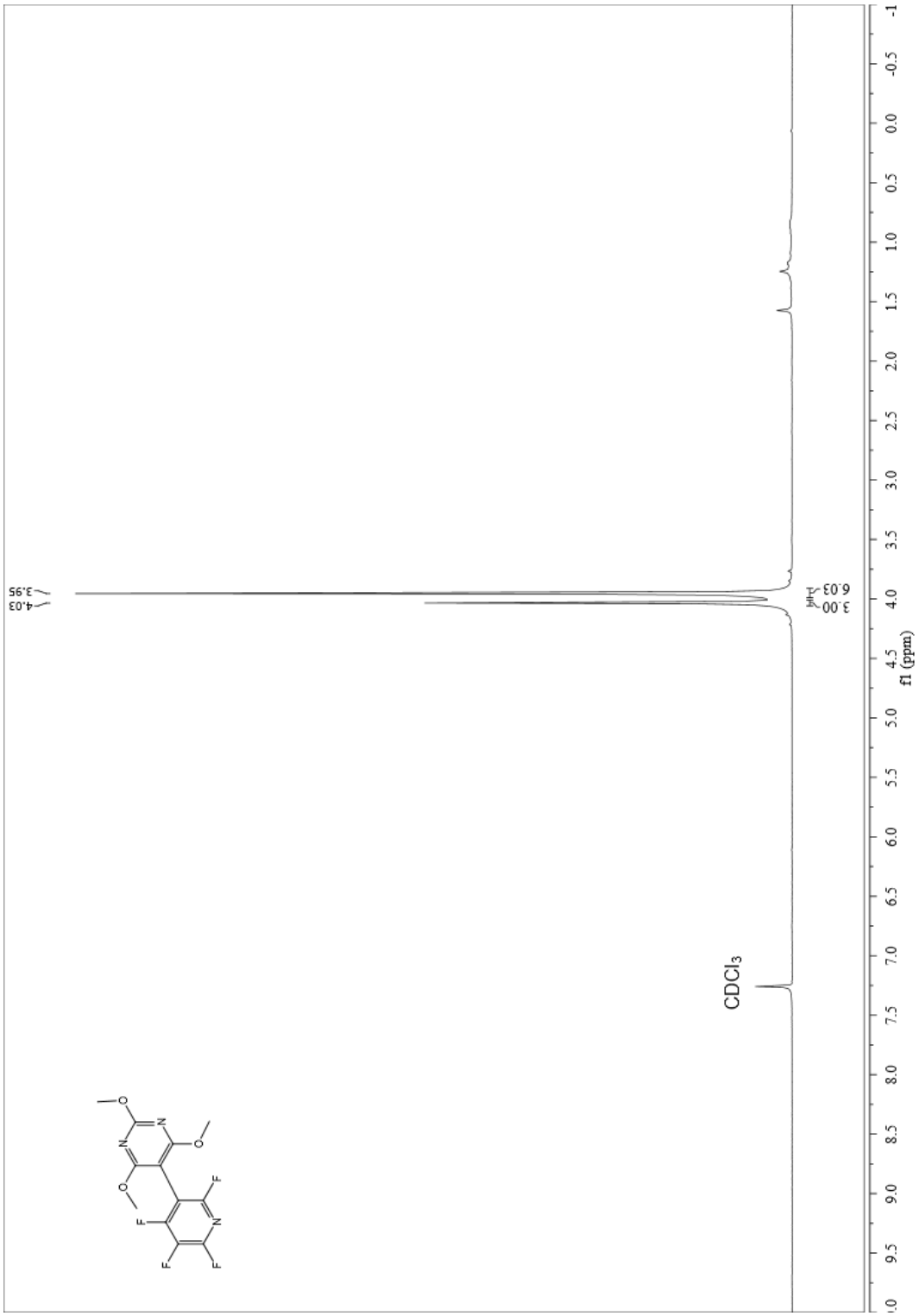




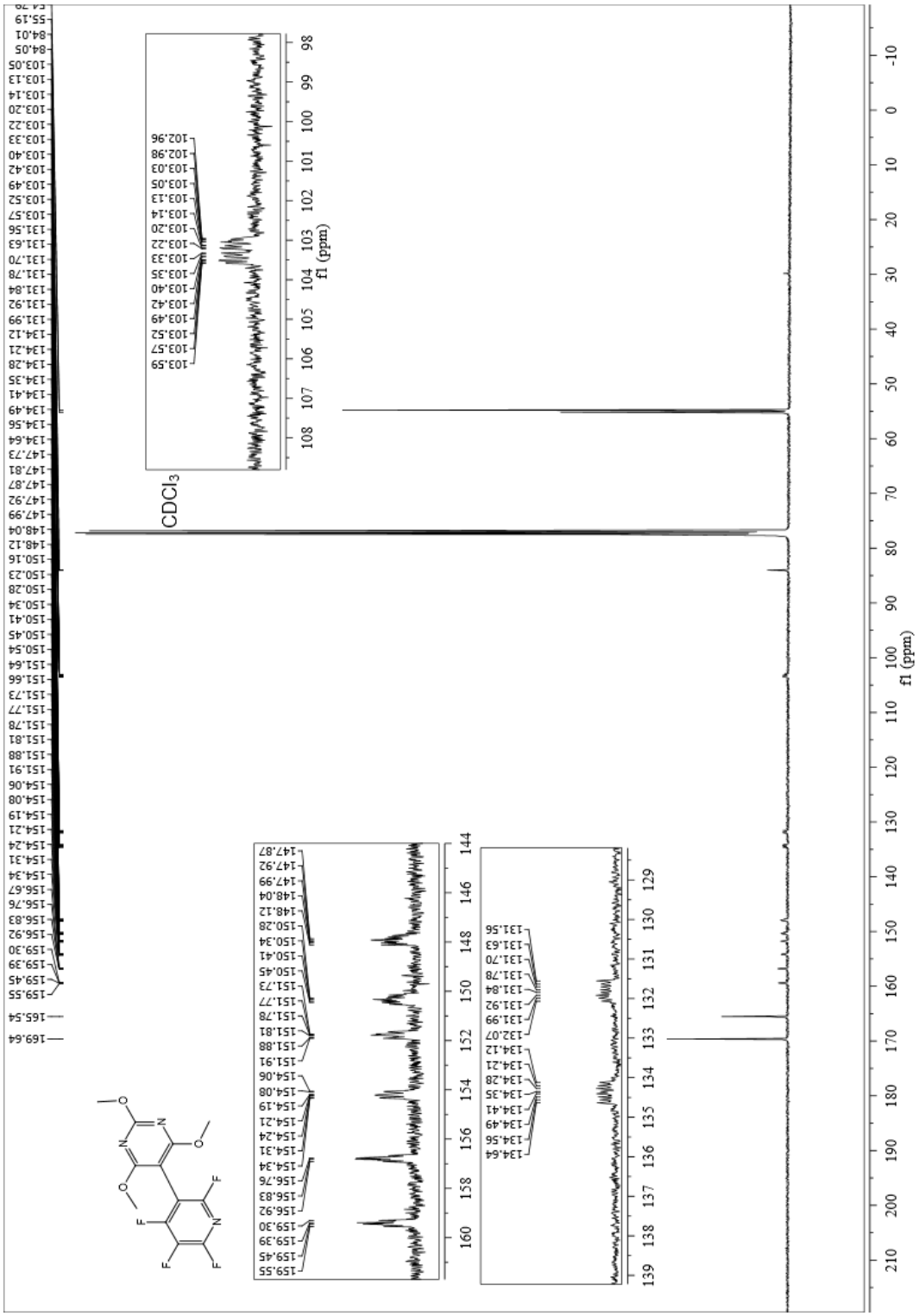
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9b (2,4,6-trimethoxy-5-(perfluoropyridin-3-yl)pyrimidine)



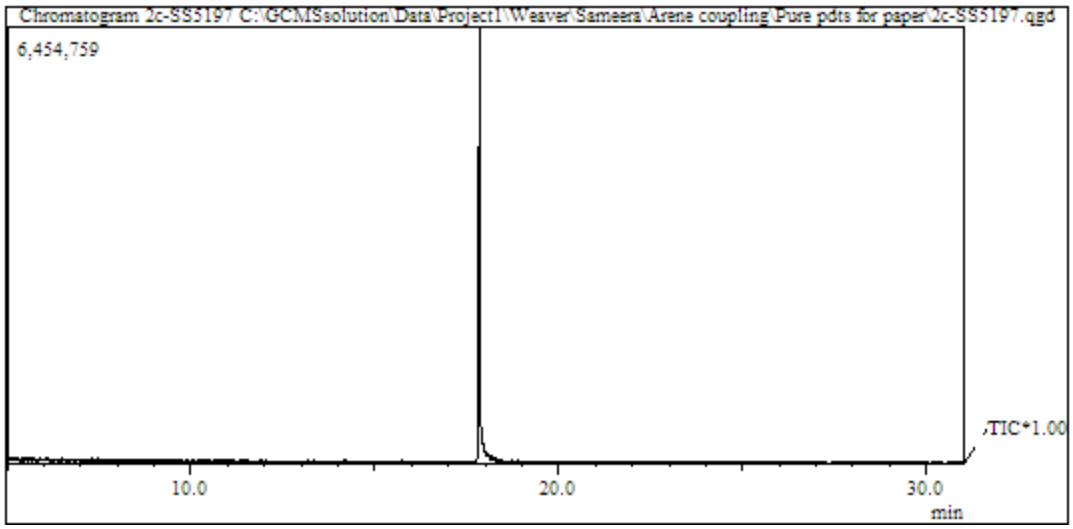
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9b (2,4,6-trimethoxy-5-(perfluoropyridin-3-yl)pyrimidine)

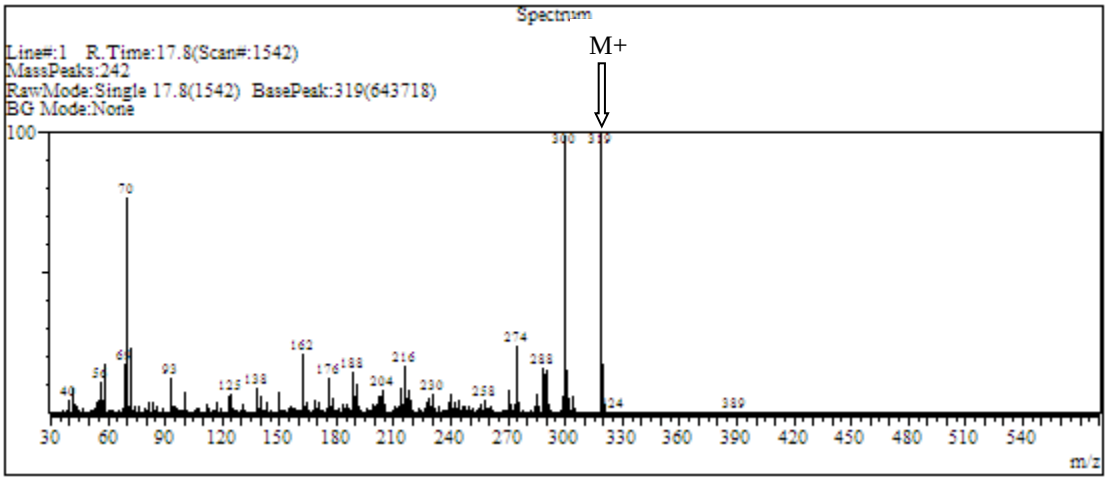


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9b (2,4,6-trimethoxy-5-(perfluoropyridin-3-yl)pyrimidine)

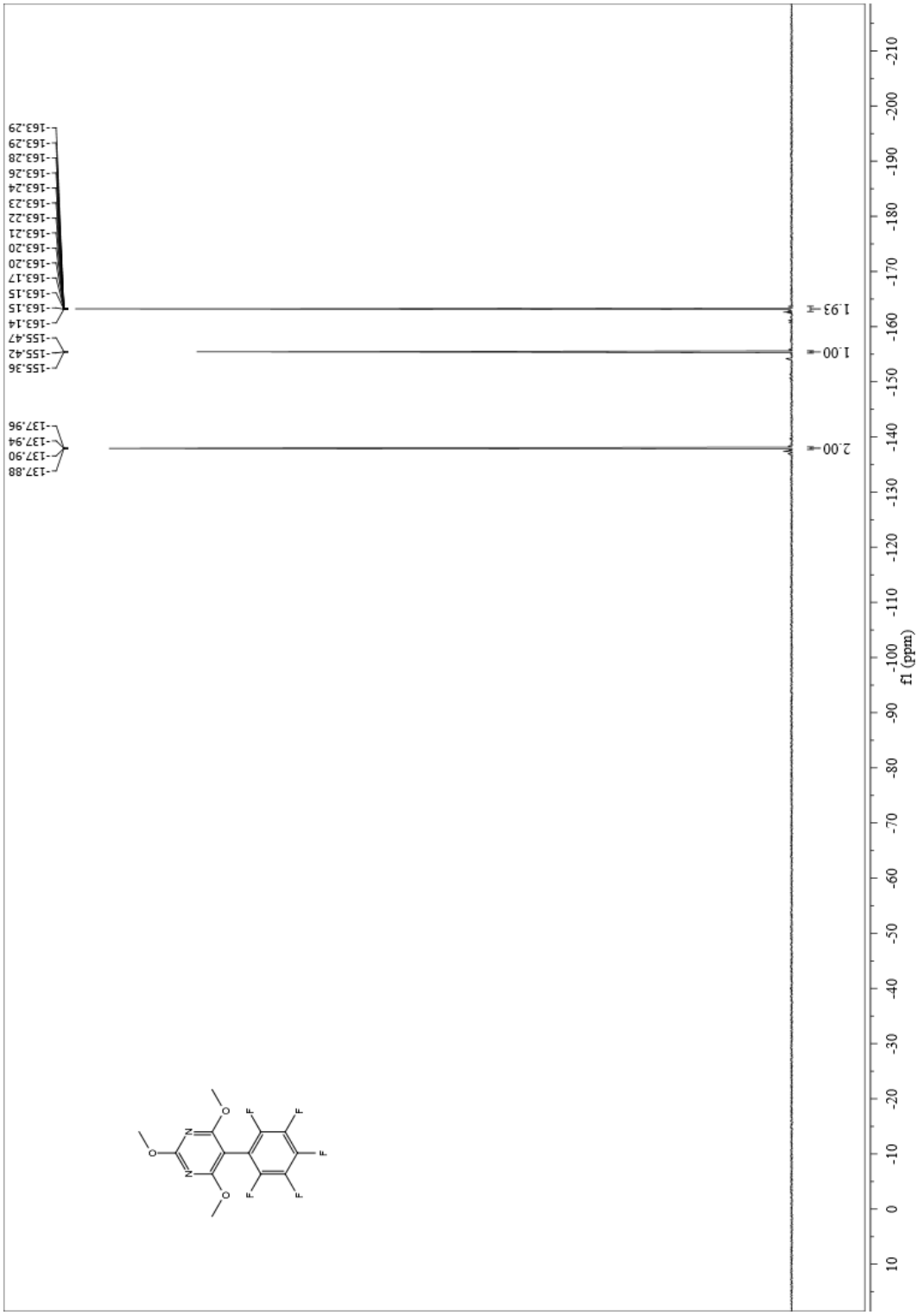


GC and MS of 3.9b (2,4,6-trimethoxy-5-(perfluoropyridin-3-yl)pyrimidine

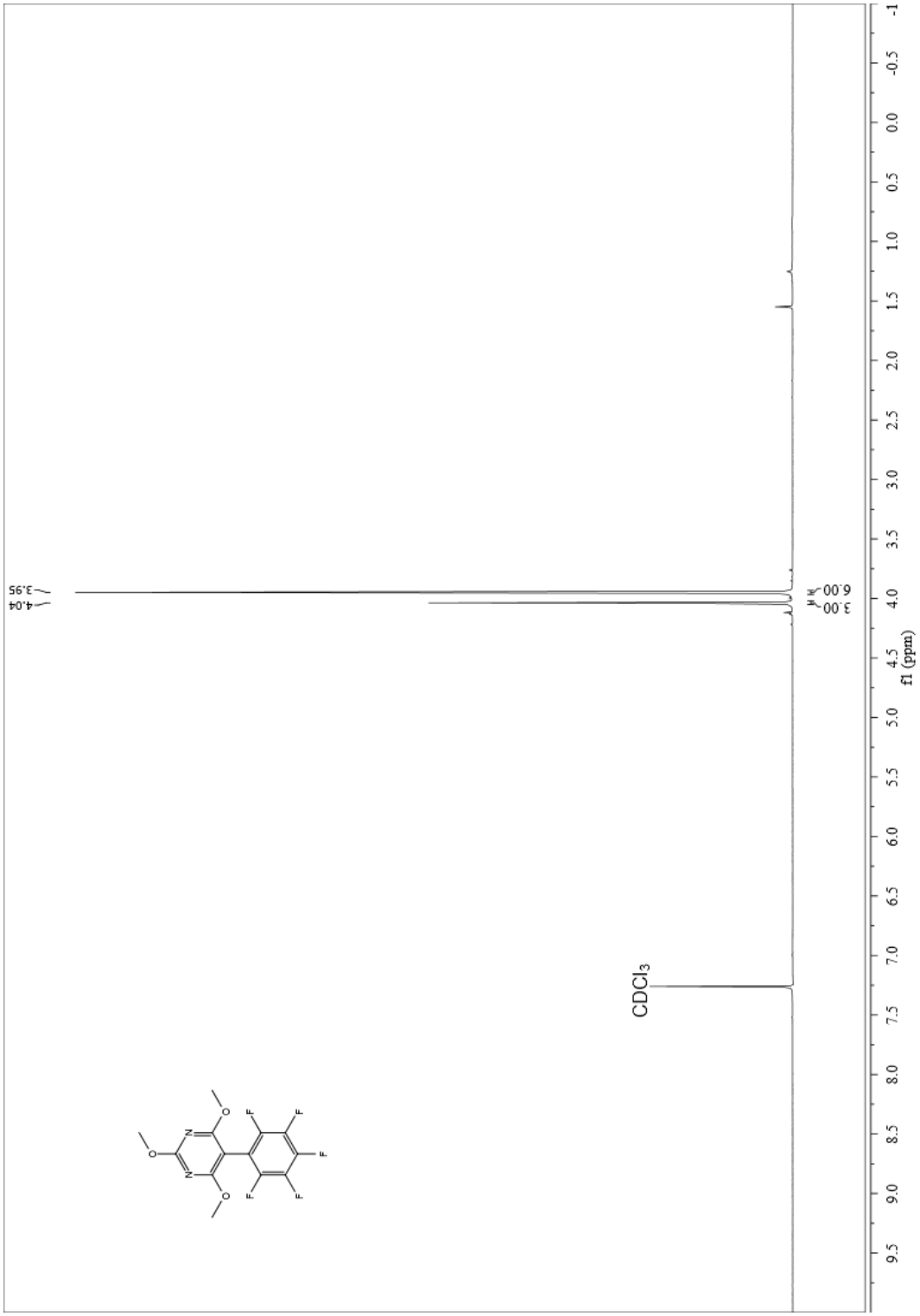




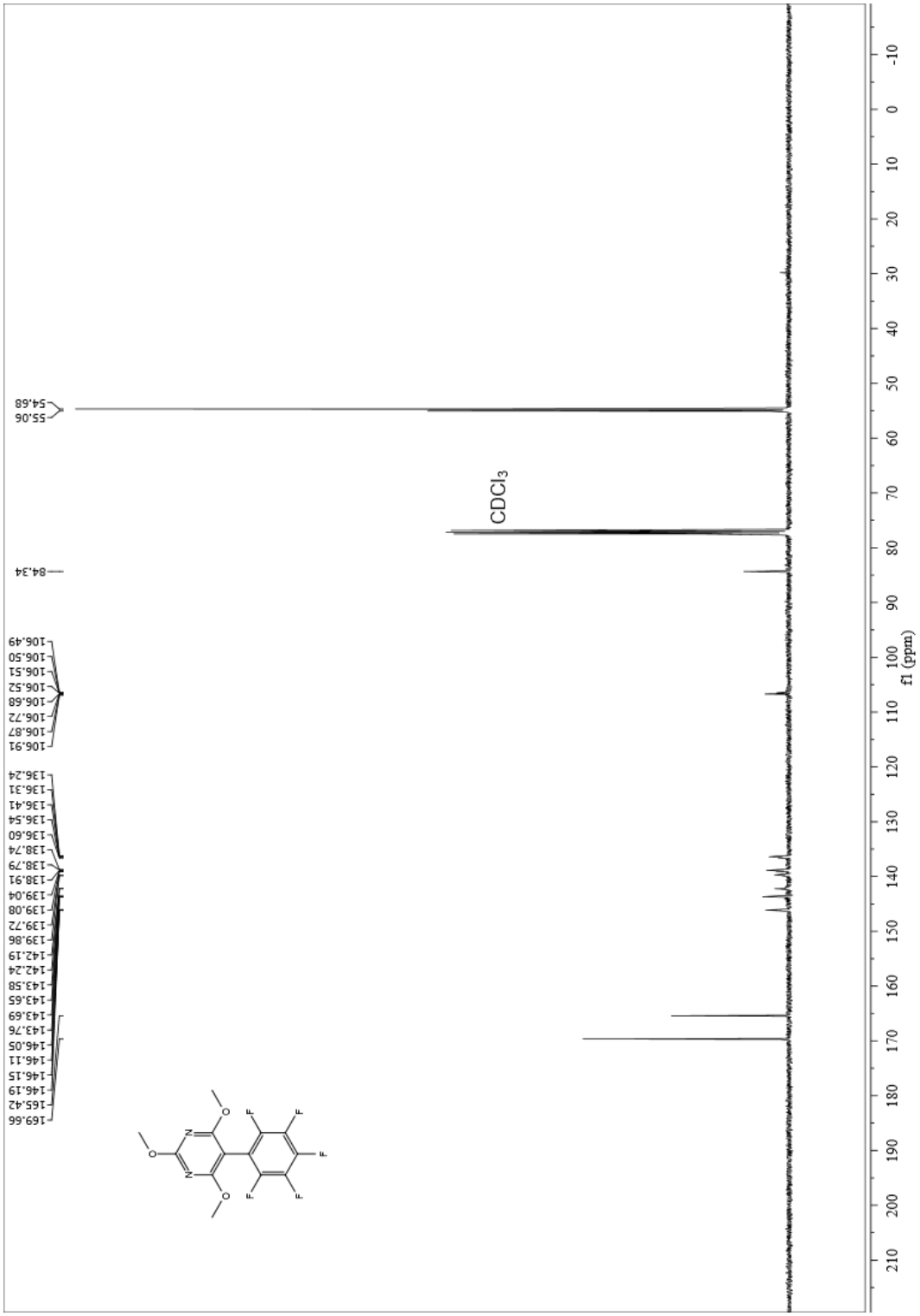
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9c (2,4,6-trimethoxy-5-(perfluorophenyl)pyrimidine)



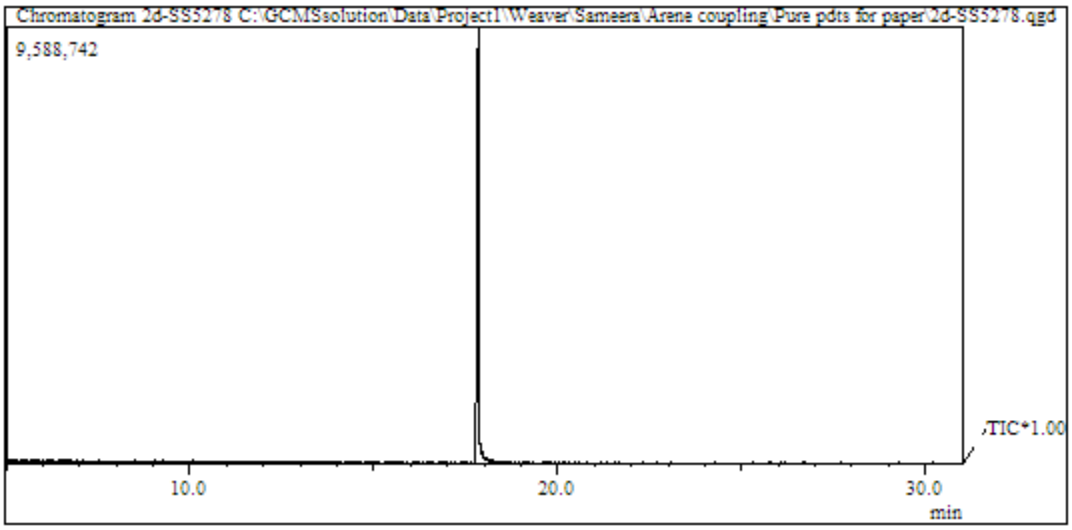
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9c (2,4,6-trimethoxy-5-(perfluorophenyl)pyrimidine)

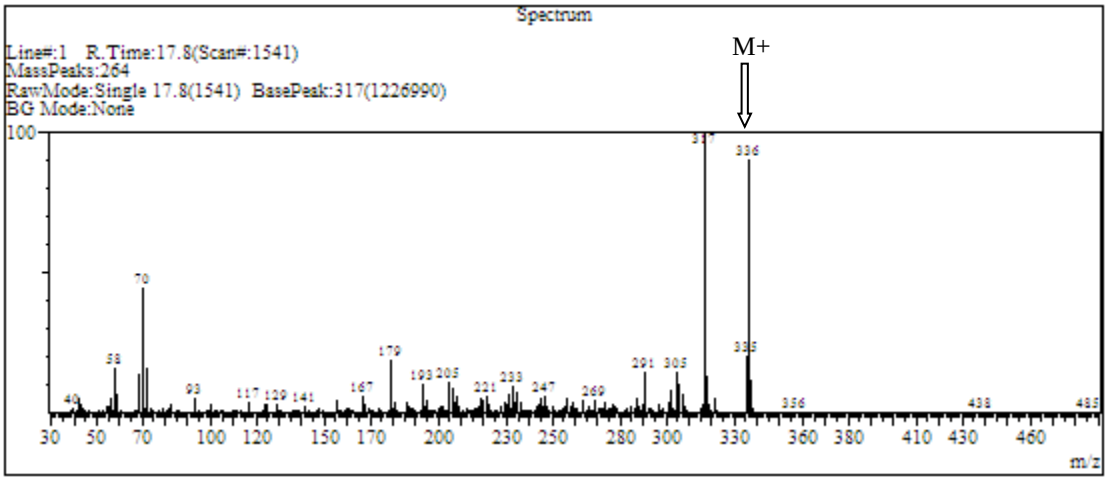


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9c (2,4,6-trimethoxy-5-(perfluorophenyl)pyrimidine)

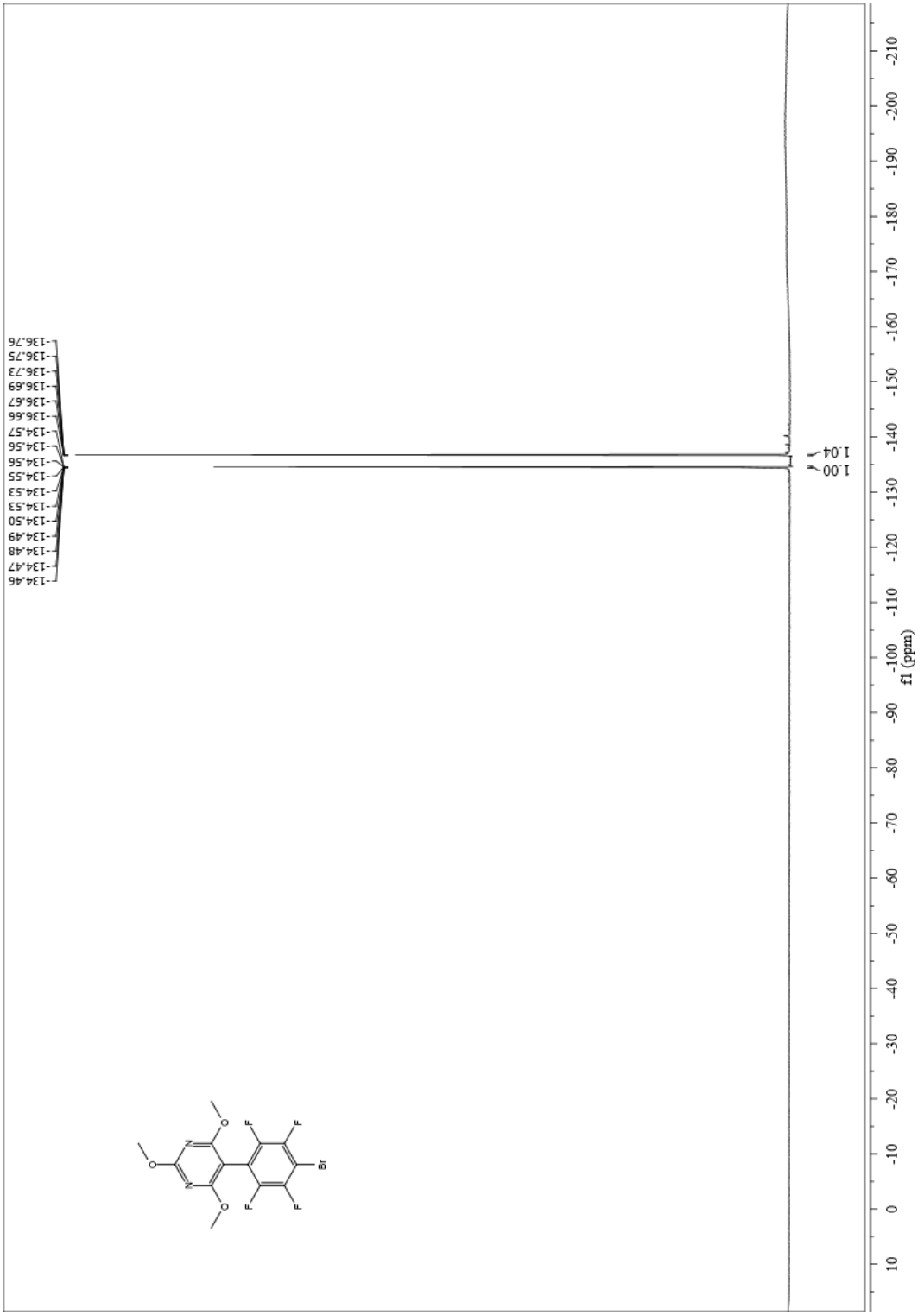


GC and MS of 3.9c (2,4,6-trimethoxy-5-(perfluorophenyl)pyrimidine)

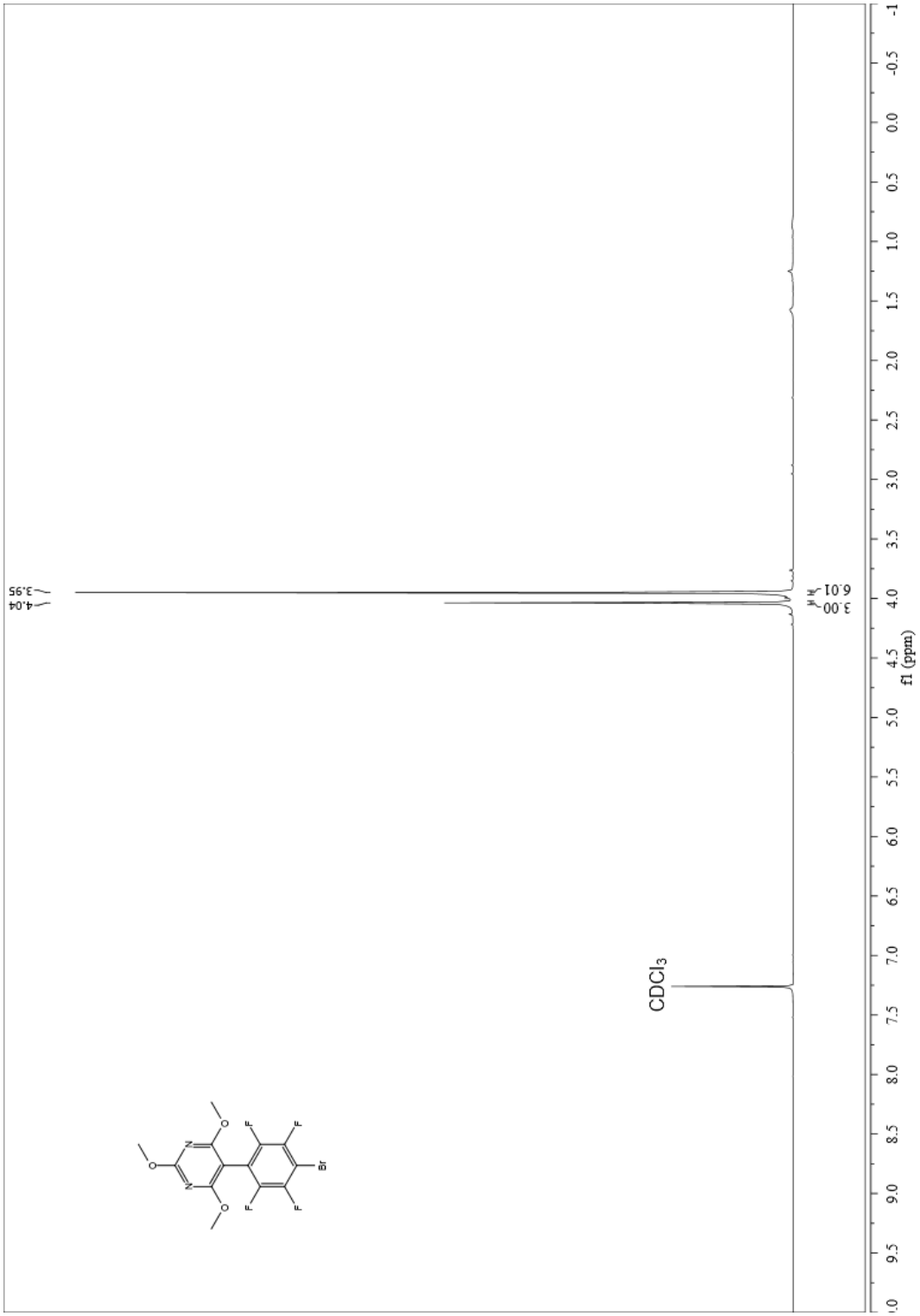




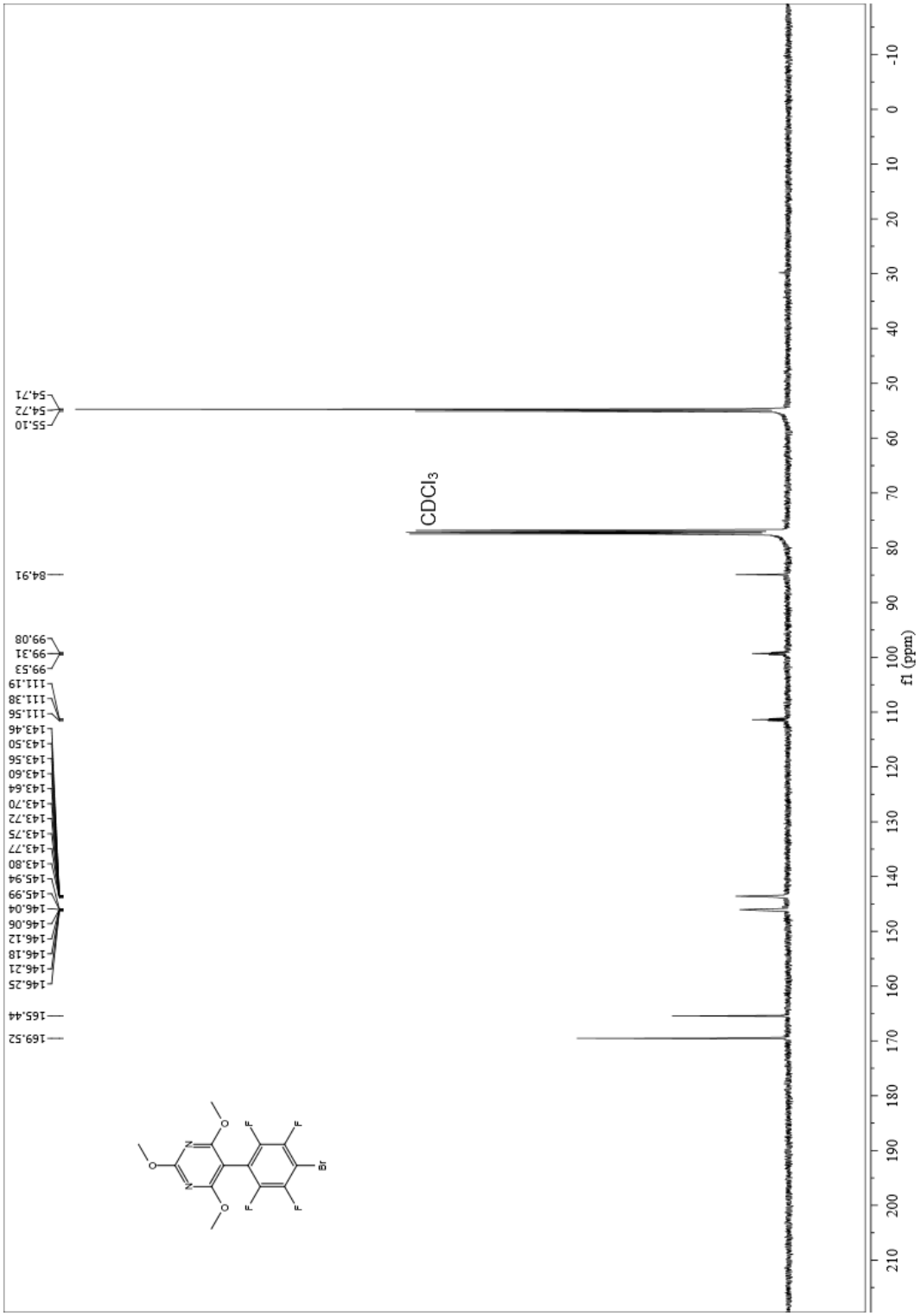
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9d (5-(4-bromo-2,3,5,6-tetrafluorophenyl)-2,4,6-trimethoxypyrimidine)



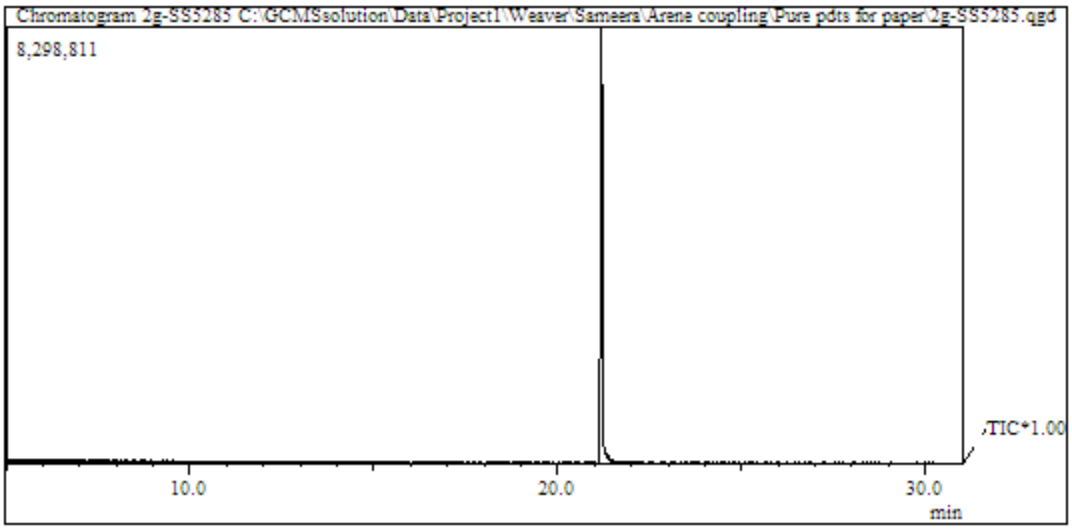
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9d (5-(4-bromo-2,3,5,6-tetrafluorophenyl)-2,4,6-trimethoxypyrimidine)

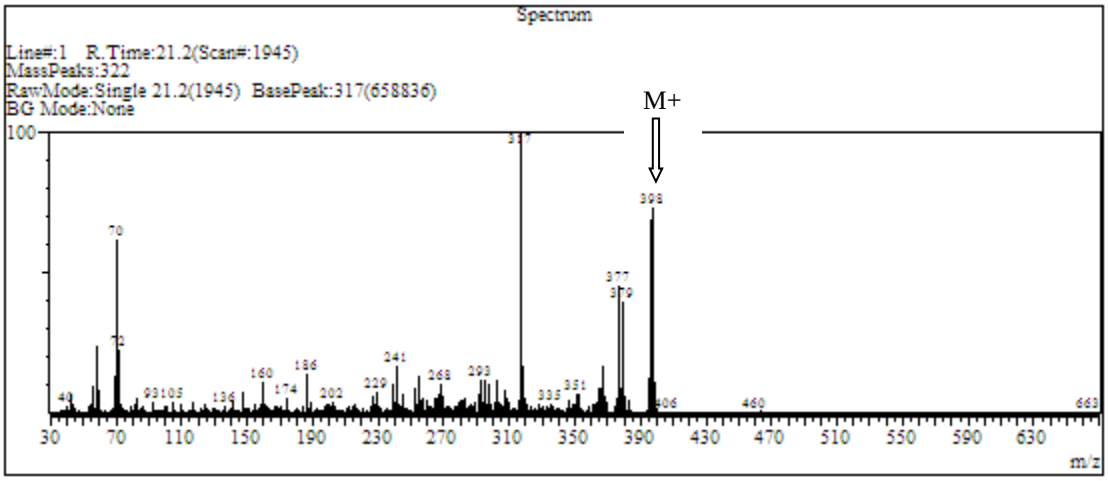


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9d (5-(4-bromo-2,3,5,6-tetrafluorophenyl)-2,4,6-trimethoxypyrimidine)

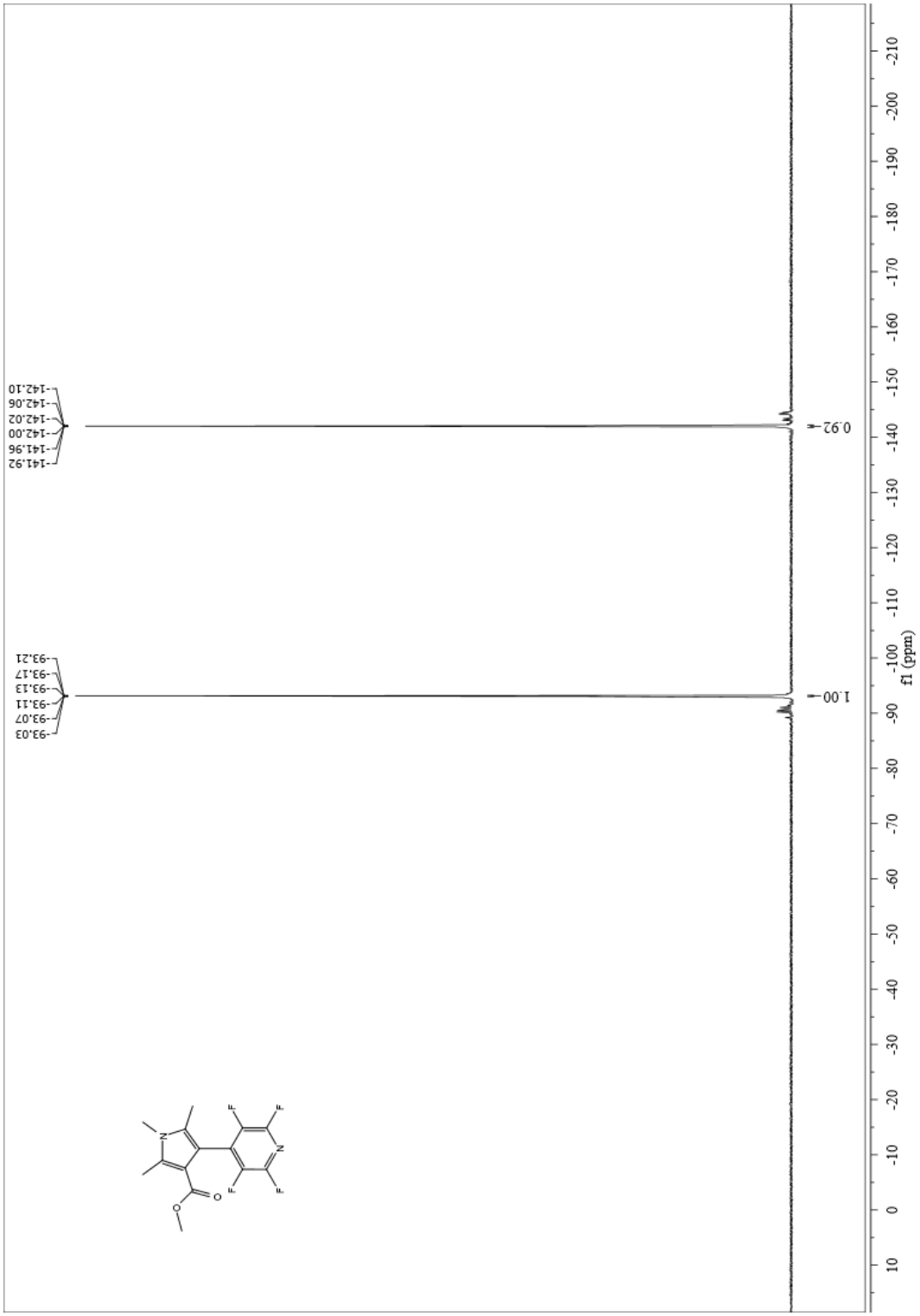


GC and MS of 3.9d (5-(4-bromo-2,3,5,6-tetrafluorophenyl)-2,4,6-trimethoxypyrimidine)

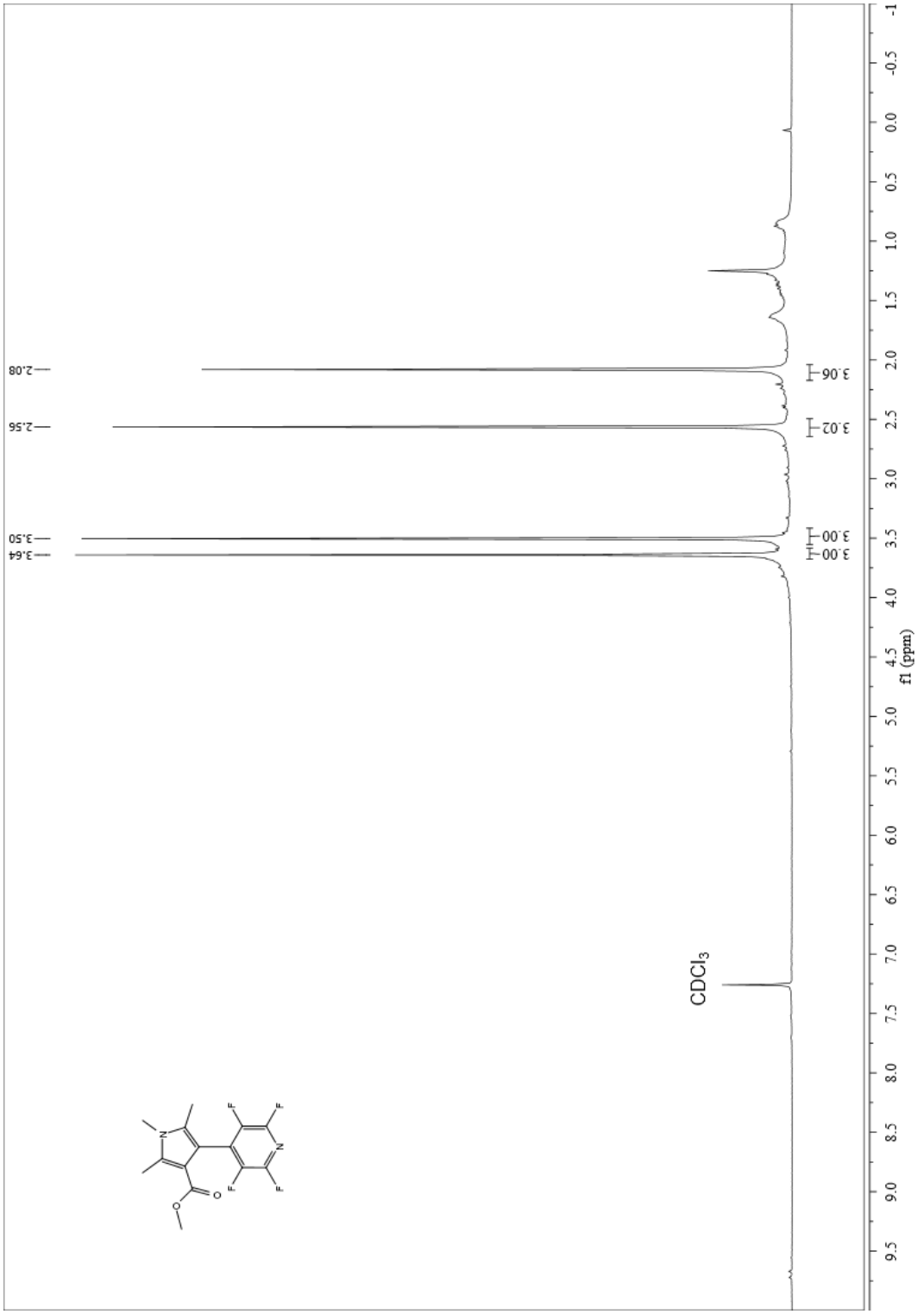




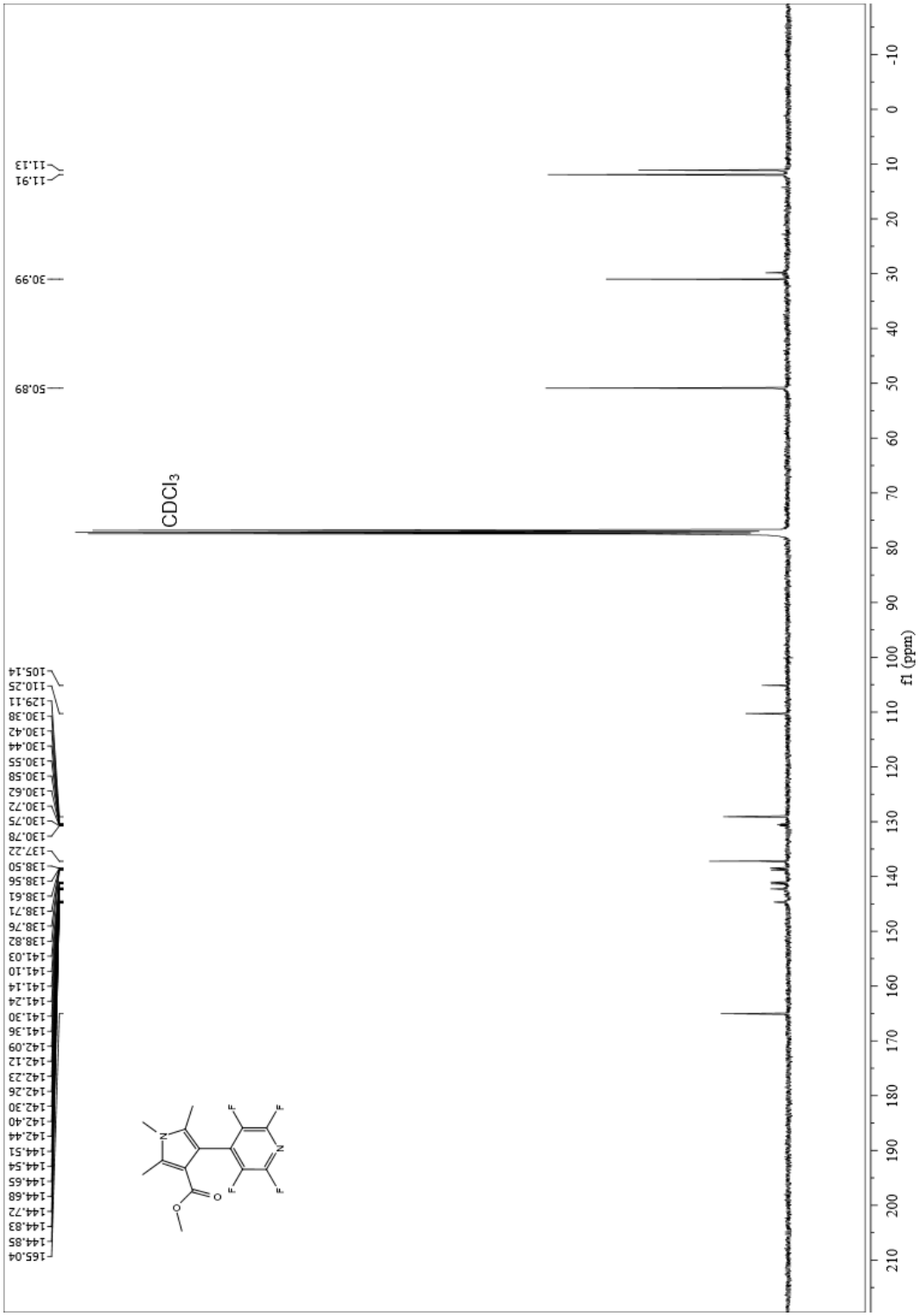
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9e (methyl 1,2,5-trimethyl-4-(perfluoropyridin-4-yl)-1H-pyrrole-3-carboxylate)



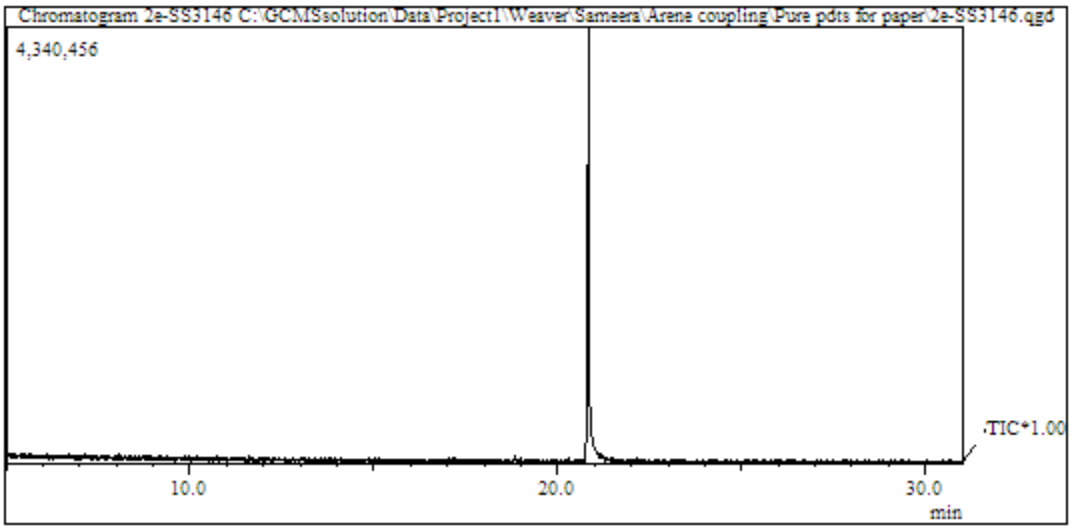
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9e (methyl 1,2,5-trimethyl-4-(perfluoropyridin-4-yl)-1H-pyrrole-3-carboxylate)

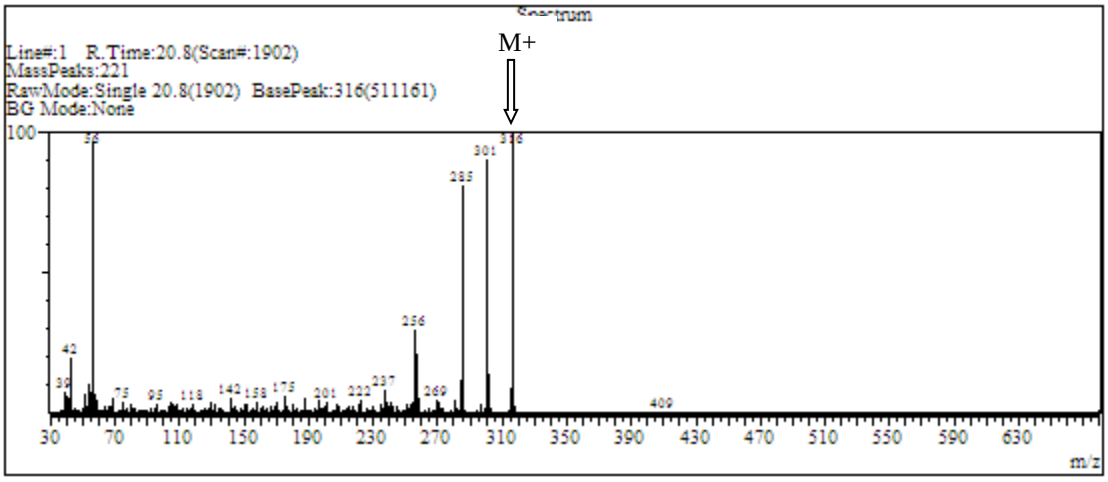


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9e (methyl 1,2,5-trimethyl-4-(perfluoropyridin-4-yl)-1H-pyrrole-3-carboxylate)

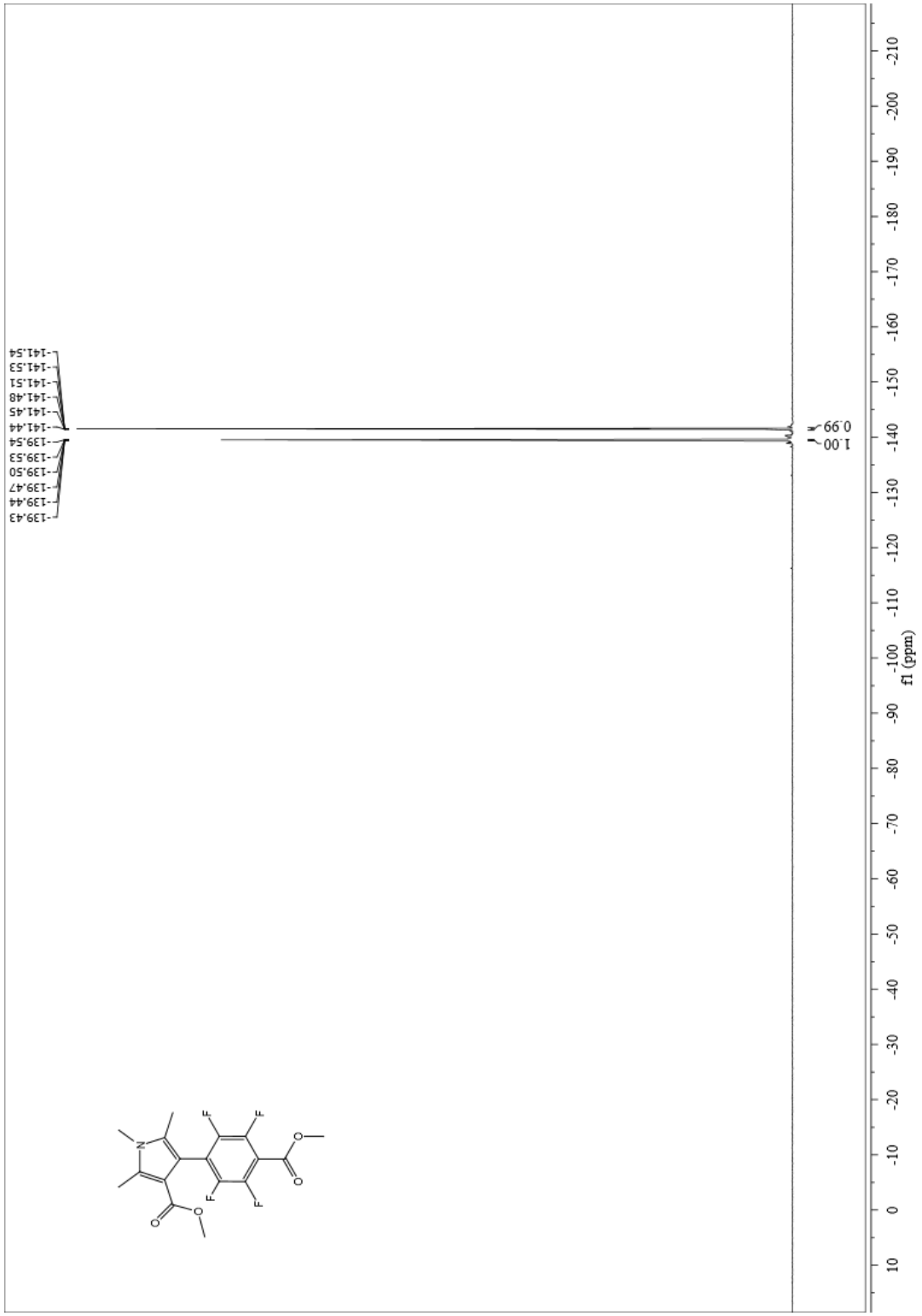


GC and MS of 3.9e (methyl 1,2,5-trimethyl-4-(perfluoropyridin-4-yl)-1H-pyrrole-3-carboxylate)

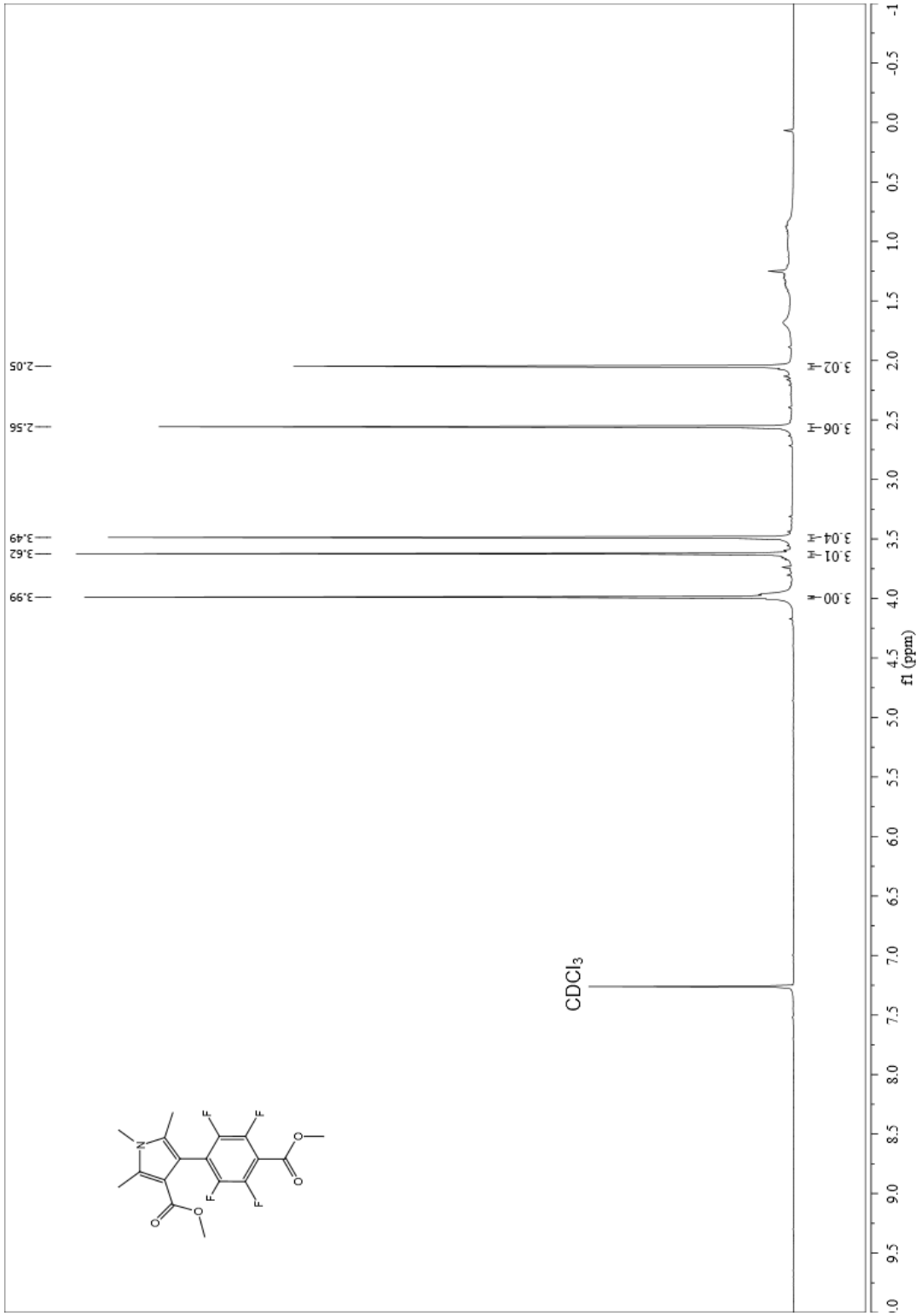




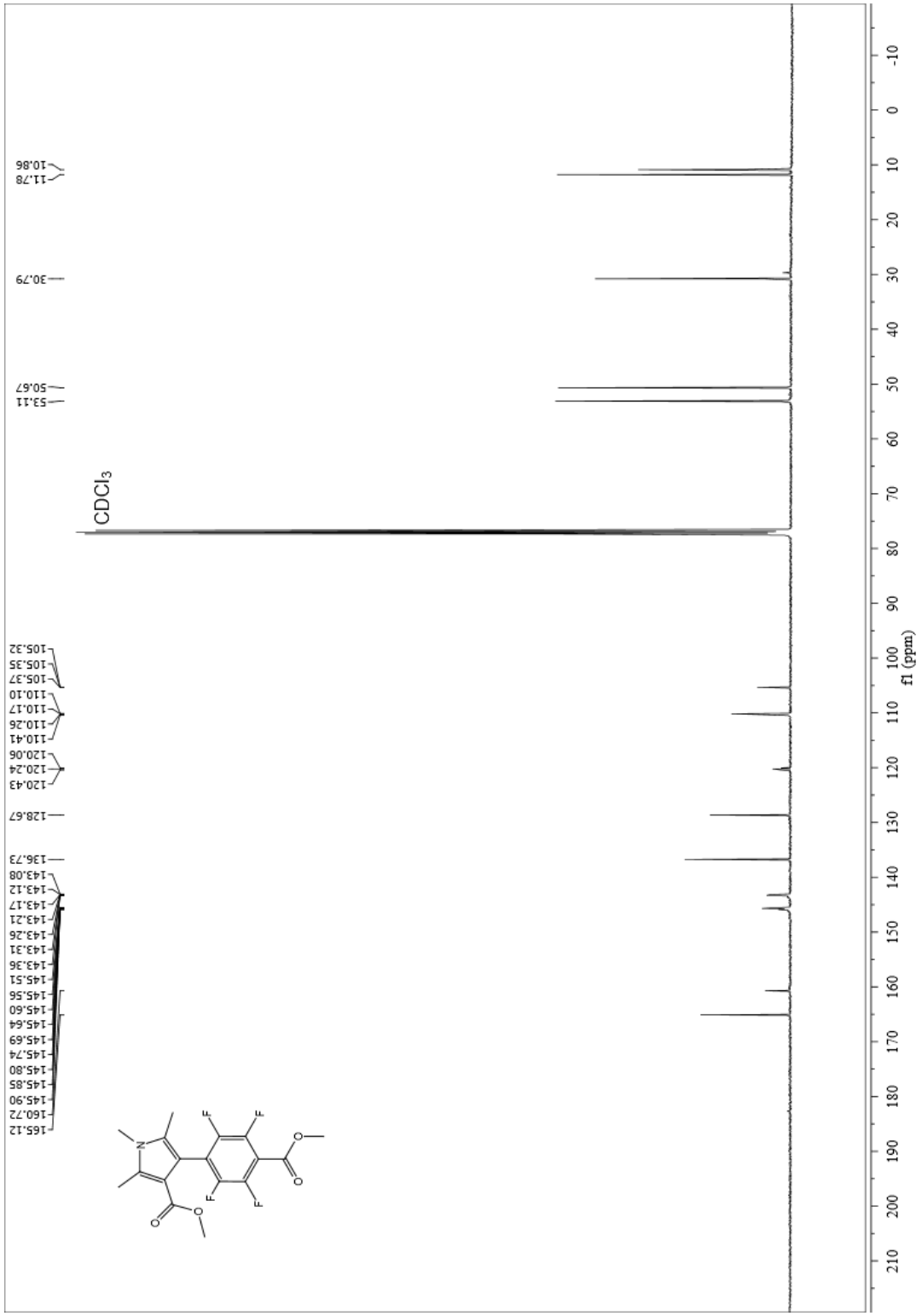
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9f (methyl 1,2,5-trimethyl-4-(2,3,5,6-tetrafluoro-4(methoxycarbonyl)phenyl)-1H-pyrrole-3-carboxylate)



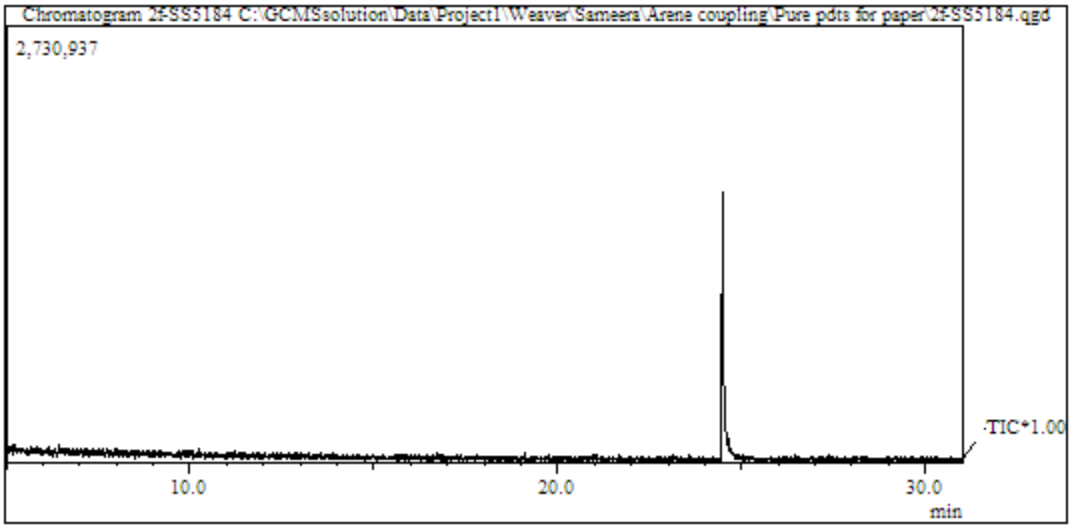
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9f (methyl 1,2,5-trimethyl-4-(2,3,5,6-tetrafluoro-4(methoxycarbonyl)phenyl)-1H-pyrrole-3-carboxylate)

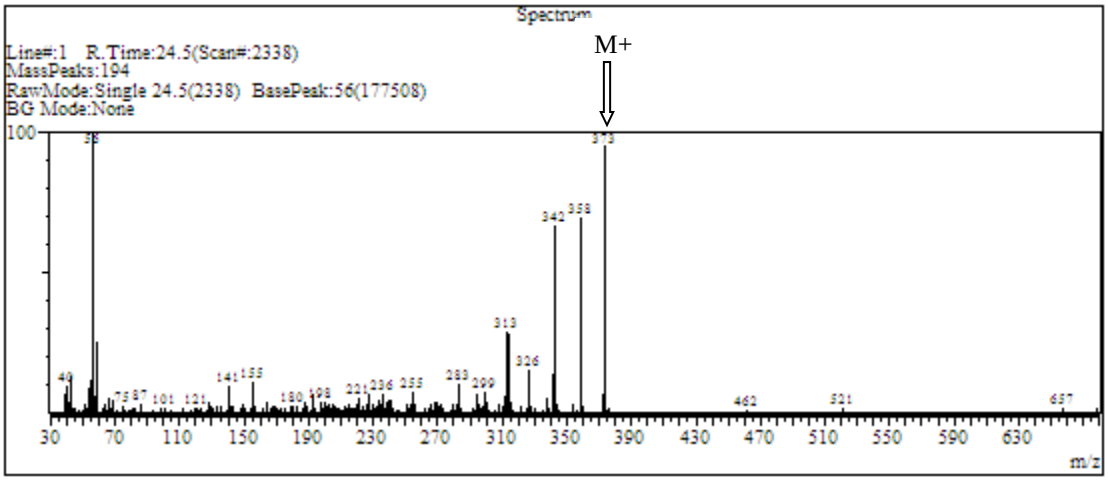


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.9f (methyl 1,2,5-trimethyl-4-(2,3,5,6-tetrafluoro-4(methoxycarbonyl)phenyl)-1H-pyrrole-3-carboxylate)

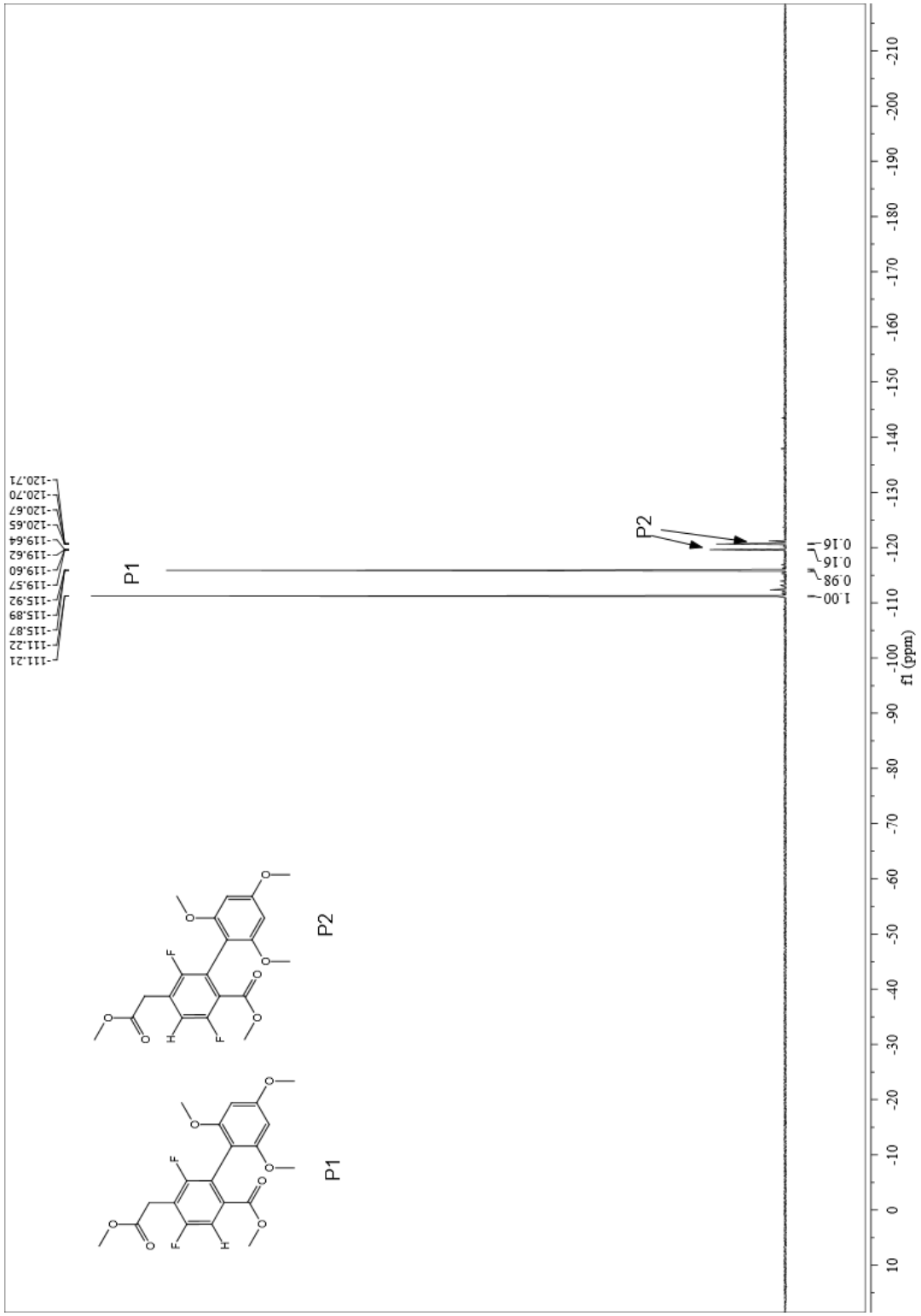


GC and MS of 3.9f (methyl 1,2,5-trimethyl-4-(2,3,5,6-tetrafluoro-4(methoxycarbonyl)phenyl)-1H-pyrrole-3-carboxylate)

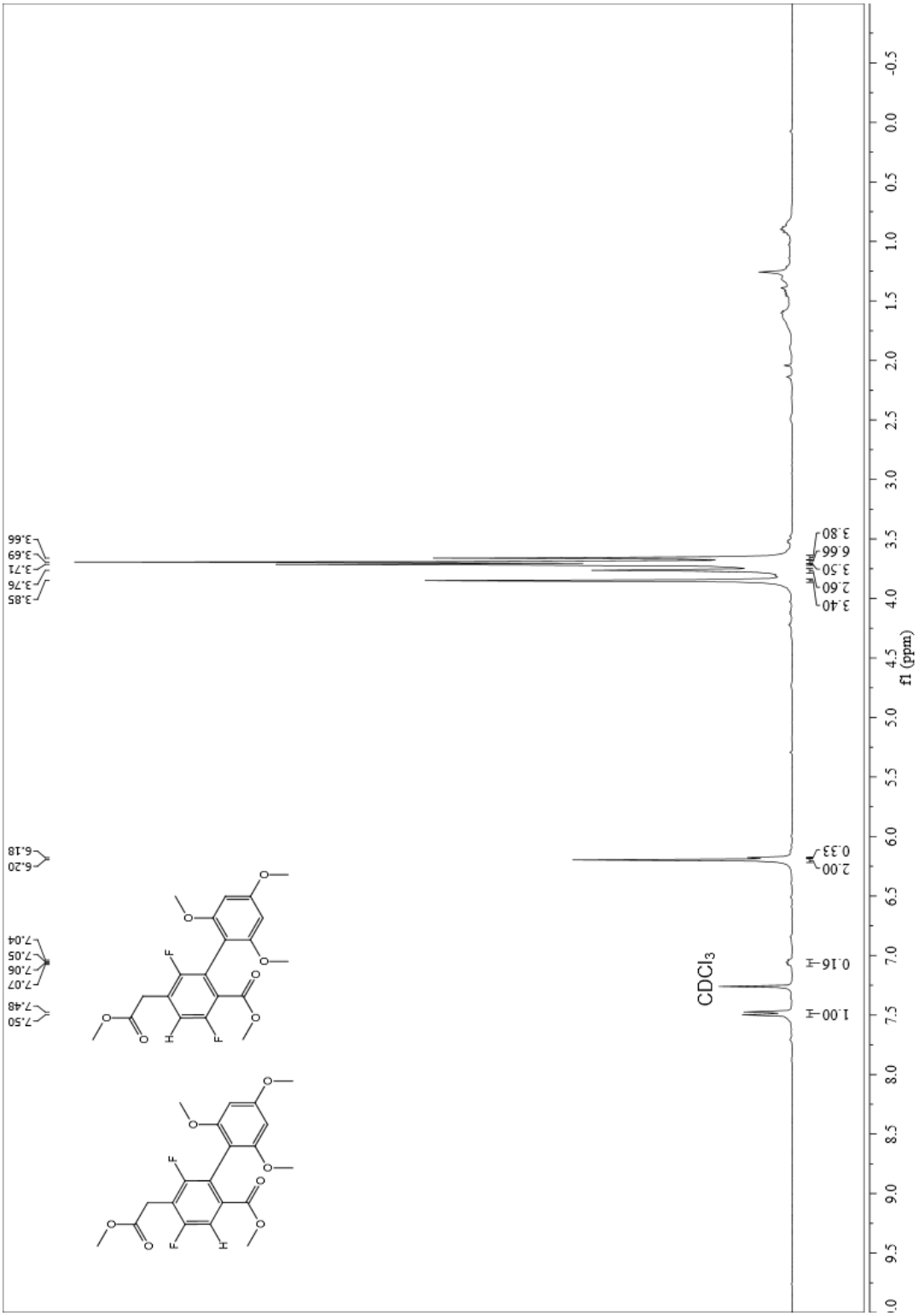




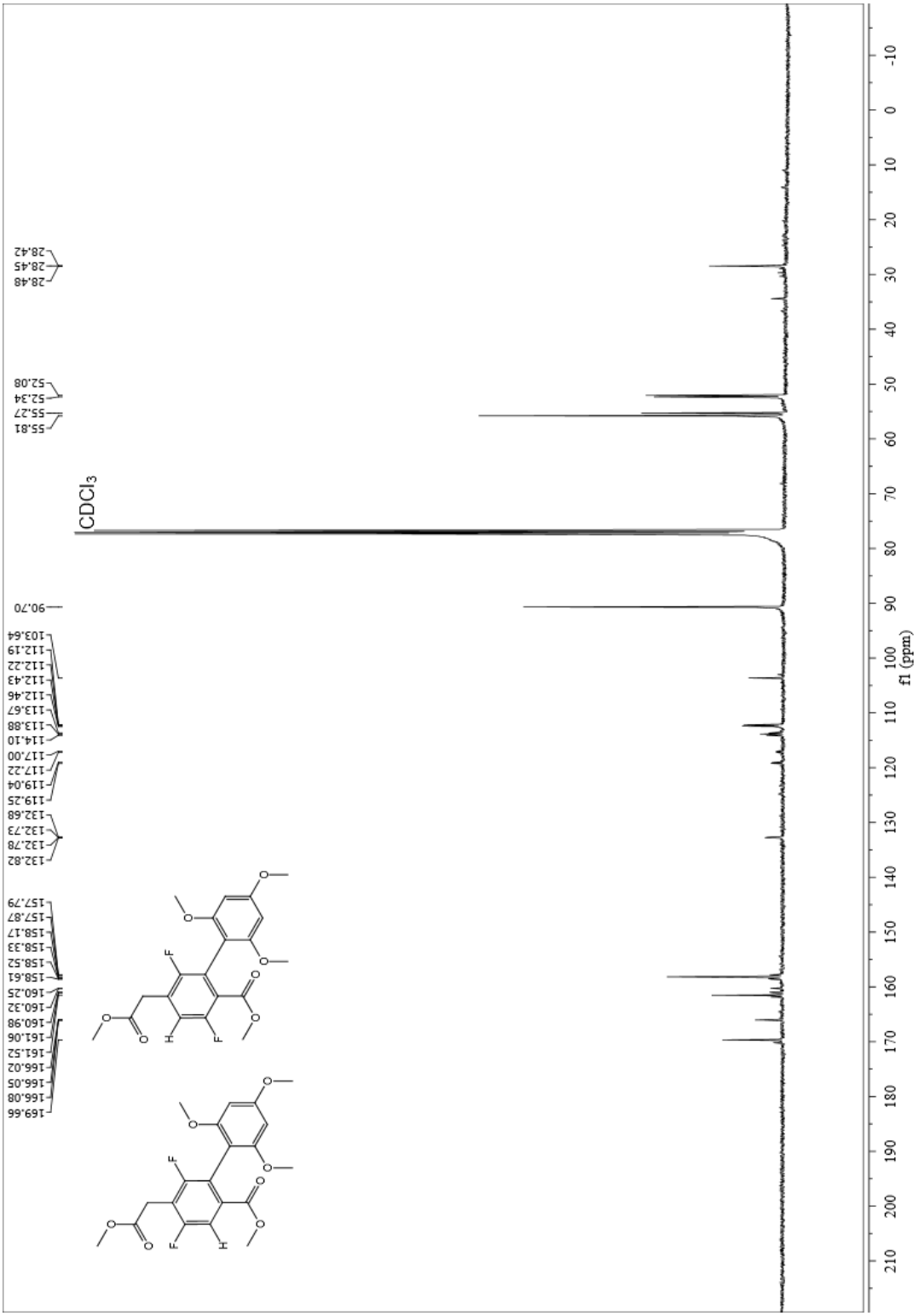
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.10c (methyl 4,6-difluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)



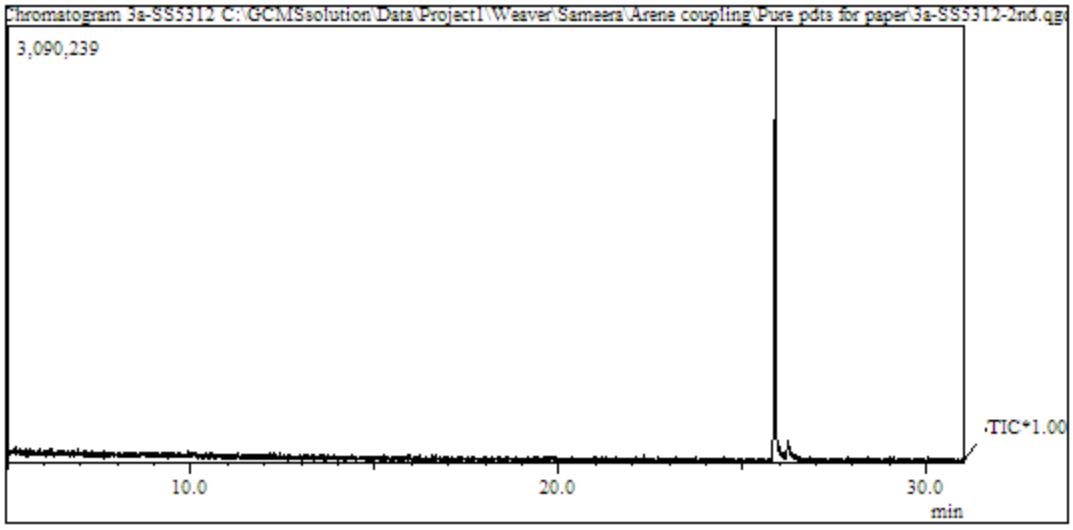
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.10c (methyl 4,6-difluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)

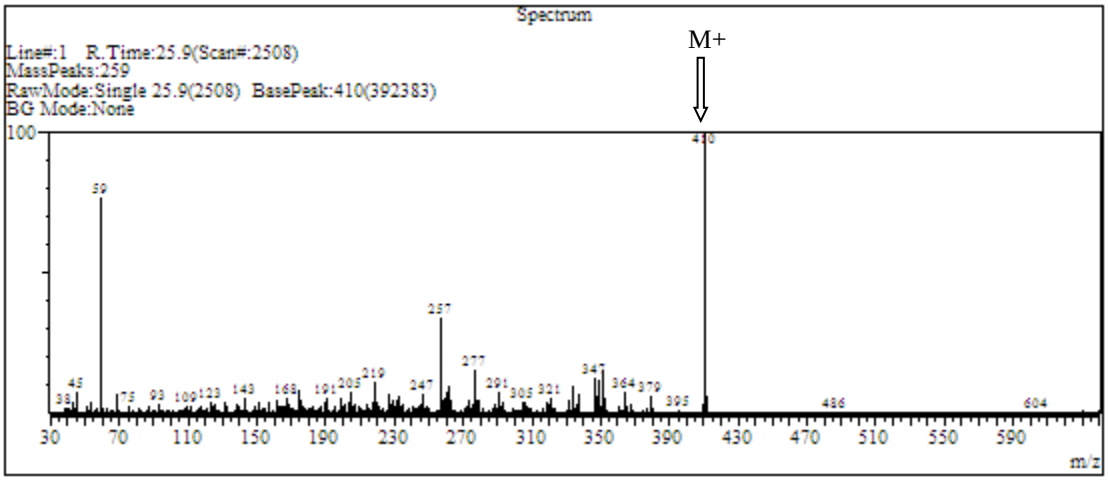


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.10c (methyl 4,6-difluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)

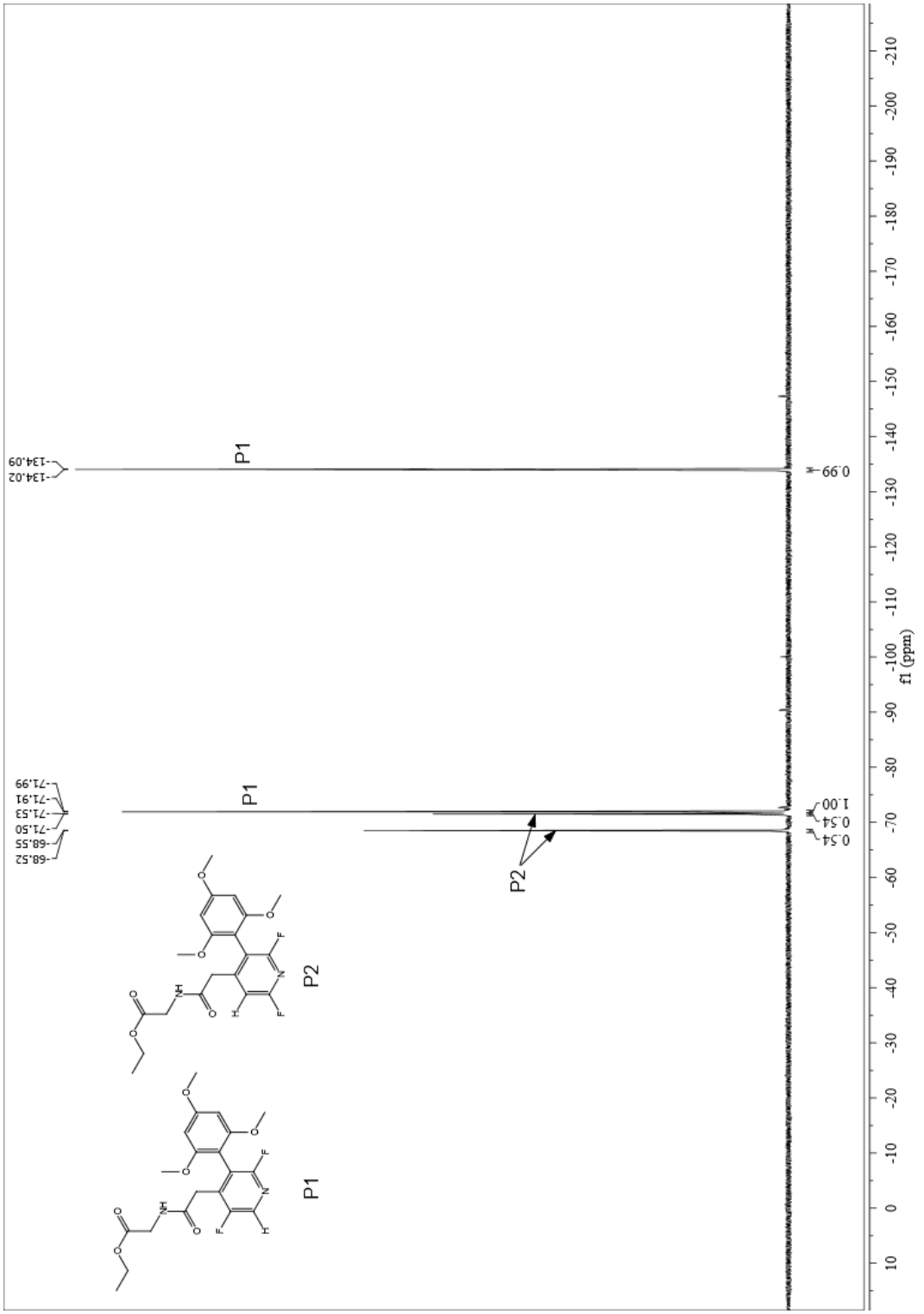


GC and MS of 3.10c (methyl 4,6-difluoro-2',4',6'-trimethoxy-5-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-2-carboxylate)

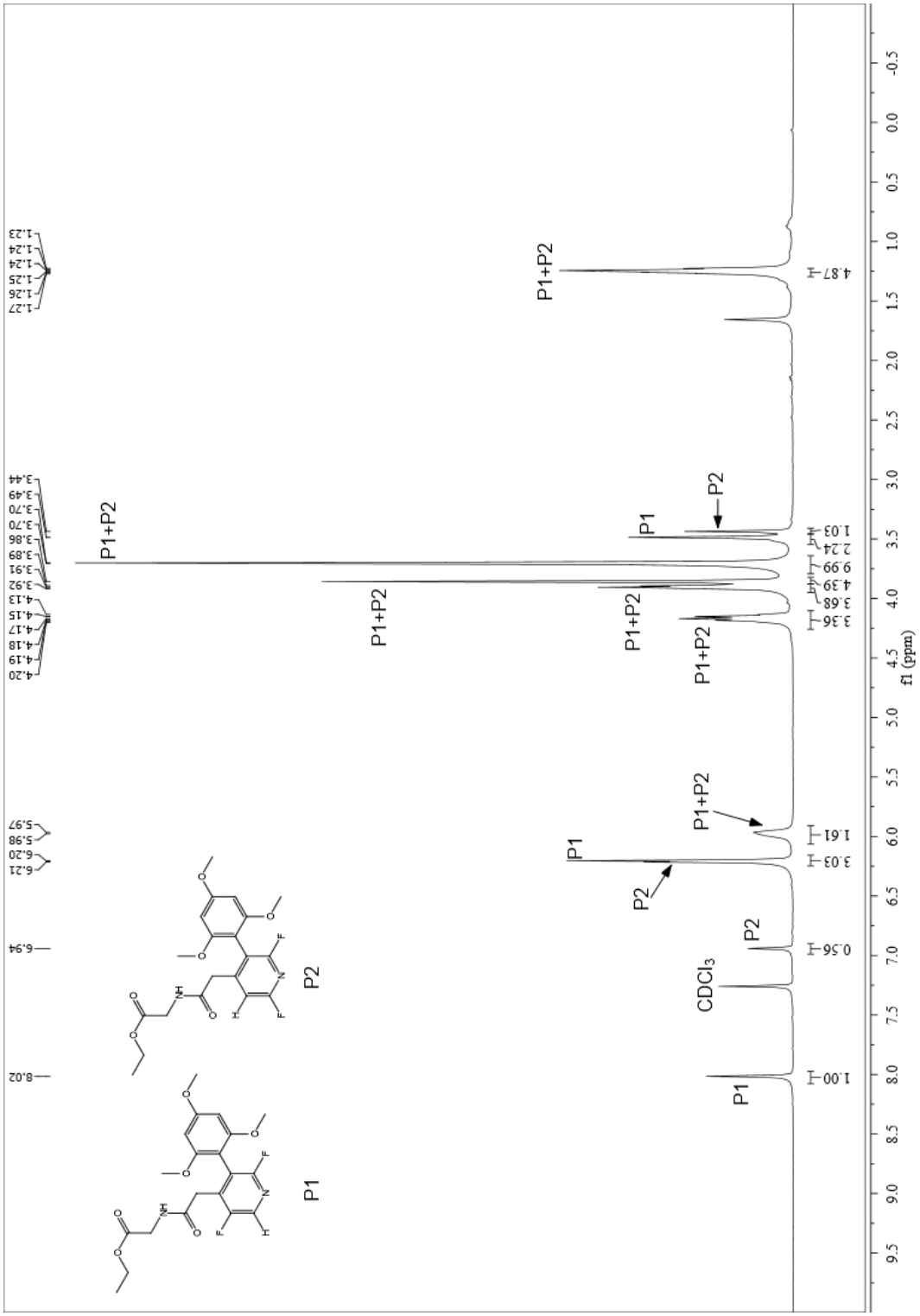




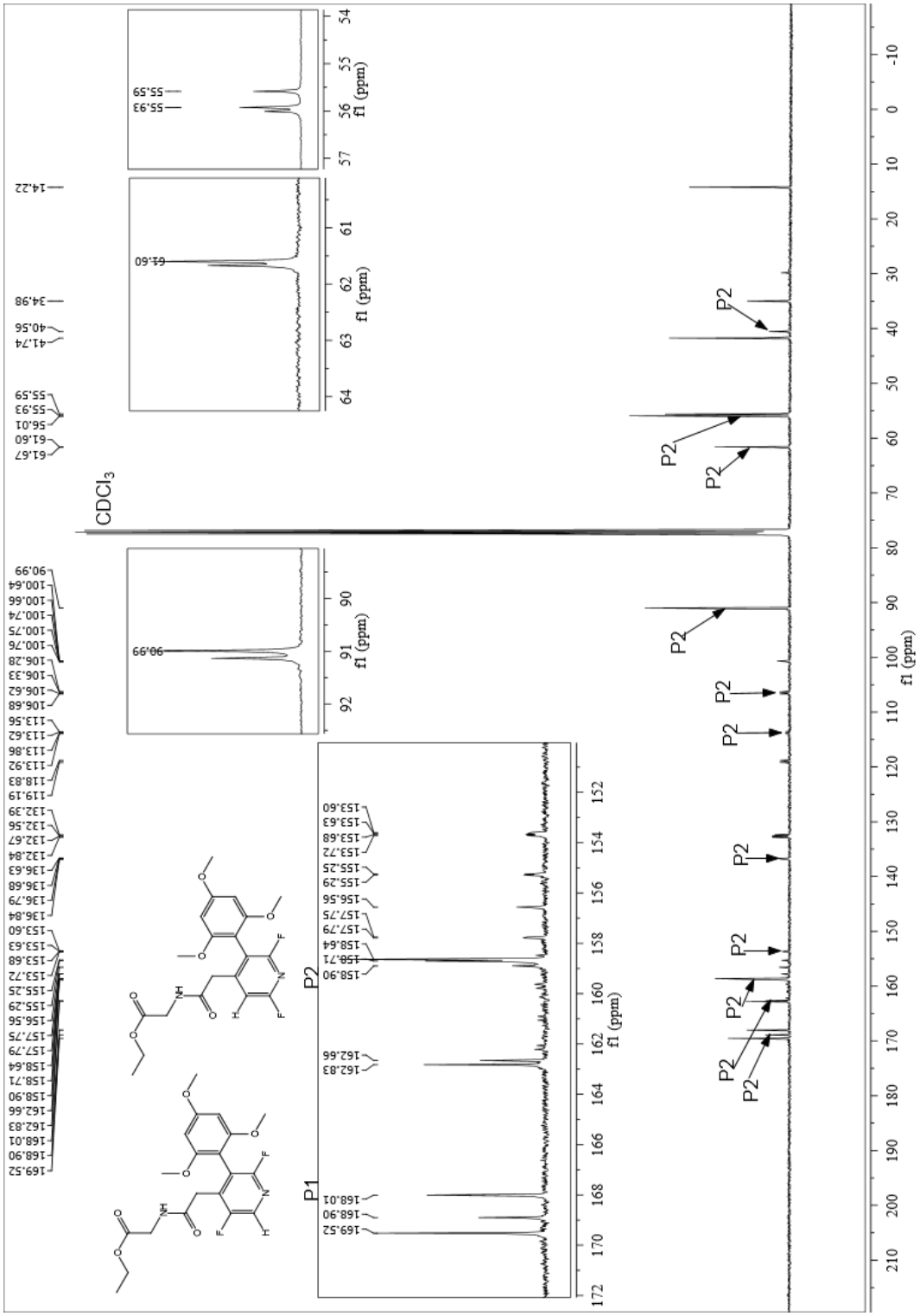
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.10f (ethyl (2-(2,5-difluoro-3-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)



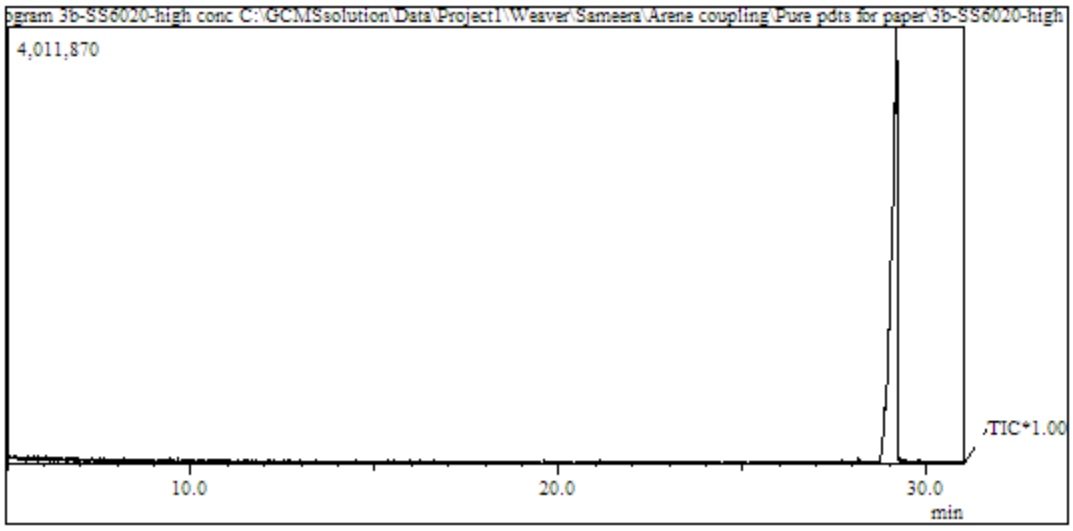
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.10f (ethyl (2-(2,5-difluoro-3-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)

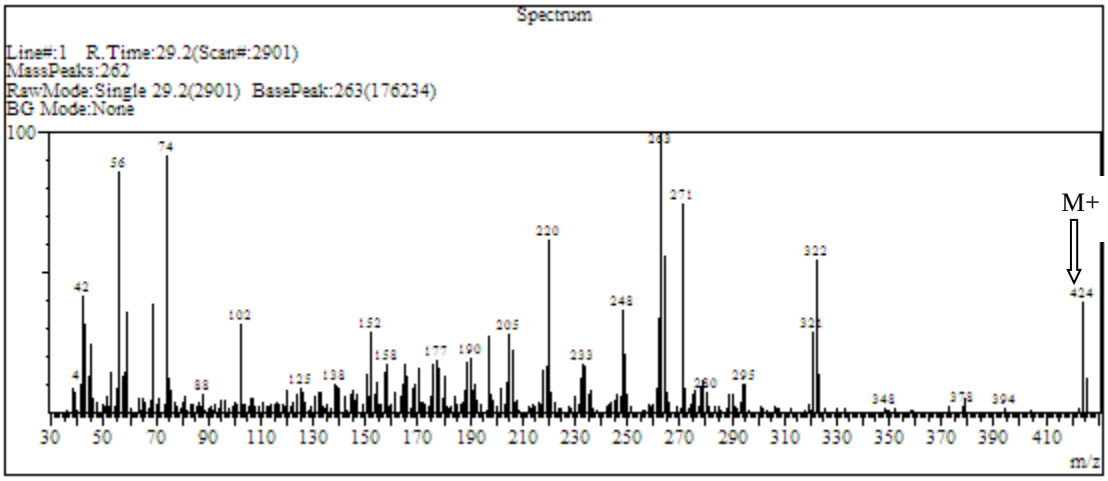


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3.10f (ethyl (2-(2,5-difluoro-3-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)



GC and MS of 3.10f (ethyl (2-(2,5-difluoro-3-(2,4,6-trimethoxyphenyl)pyridin-4-yl)acetyl)glycinate)





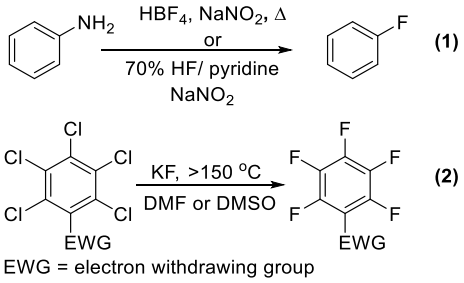
CHAPTER IV

NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS TO ACCESS FUNCTIONALIZED FLUOROAROMATICS

4.1 Introduction to functionalized fluoroaromatics

Perfluoaromatics can be considered as one of the most abundant and the cheapest class among all the polyfluoroaromatics. For instance, pentafluoropyridine costs $ 945/mol[80] while simply replacing one fluorine with a hydrogen, 2,3,5,6-tetrafluoropyridine, drives the cost to $7015/mol[81] at Sigma-Aldrich. The two most common industrially utilized routes for the synthesis of fluoroaromatics are the Balz-Schiemann[82] reaction and the Halex[83] reaction. The Balz-Schiemann reaction is used to install a single fluorine per NH_2 group *via* diazotization of an aromatic amine in anhydrous HF and subsequent decomposition of the resultant aryldiazonium fluoride (Scheme 4.1, eq 1).[84] The acidic conditions, the toxicity of the reagents, and the potential for explosions limit the large scale utility of the Balz-Schiemann reaction.[85] The halogen exchange (Halex) reaction, is however, the most preferred process to form aromatic C−F bonds (eq 2).[15] In contrast to the Balz-Schiemann reaction, the Halex process generates per and

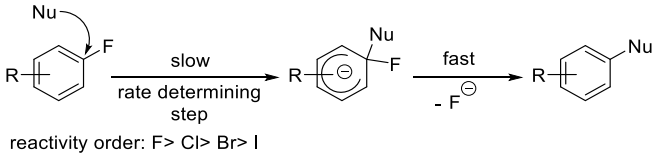
polyfluoroarenes by exhaustive fluoride substitution of C–Cl bonds. In the process, C–Cl bonds are converted to C–F bonds *via* a series of S_NAr reactions with a fluoride salt. The industrial Halex reaction is carried out at high temperatures (≥150 °C) in polar, aprotic solvents such as DMSO and DMF in the presence of an inorganic fluoride salt such as KF.[15, 83] Commercially available perfluoroarenes are minimally functionalized. Presumably, this is due to the extreme conditions which do not allow much functional group tolerance.



Scheme 4.1 Common routes to fluoroaromatics

Significant efforts have been made to increase the complexity of commercially available simple perfluoroaromatics. One very common way is to use nucleophilic aromatic substitution (S_NAr) with variety of oxygen-, nitrogen-, carbon-, and sulfur- based nucleophiles.[86] Aromatic fluorines inductively withdraw electron density, making the aromatic ring electrophilic such that nucleophilic substitution become possible. Generally, the S_NAr reactivity of C_{aryl}–X (where X = F, Cl, Br, I) bond decreases in the order of fluoride > chloride > bromide > iodide, which is opposite to that observed in the S_N2 reactions of aliphatic halides. The difference can be explained by considering the transition state which is a part of the addition-elimination pathway where the nucleophilic addition is rate-determining step (Scheme 4.2). Attached fluorines on the aromatic ring activate the addition step due to its relatively small steric volume, and strong electron withdrawing effect. In contrast, in the transition state for the S_N2 reaction the bond breaking event between the carbon and halogen atoms plays an important role where substantial bond breaking occurs in the transition state for the S_N2 reaction. Consequently, aliphatic iodides

react fastest among the aliphatic halides since they are the most stable anion and easily polarized.[87]

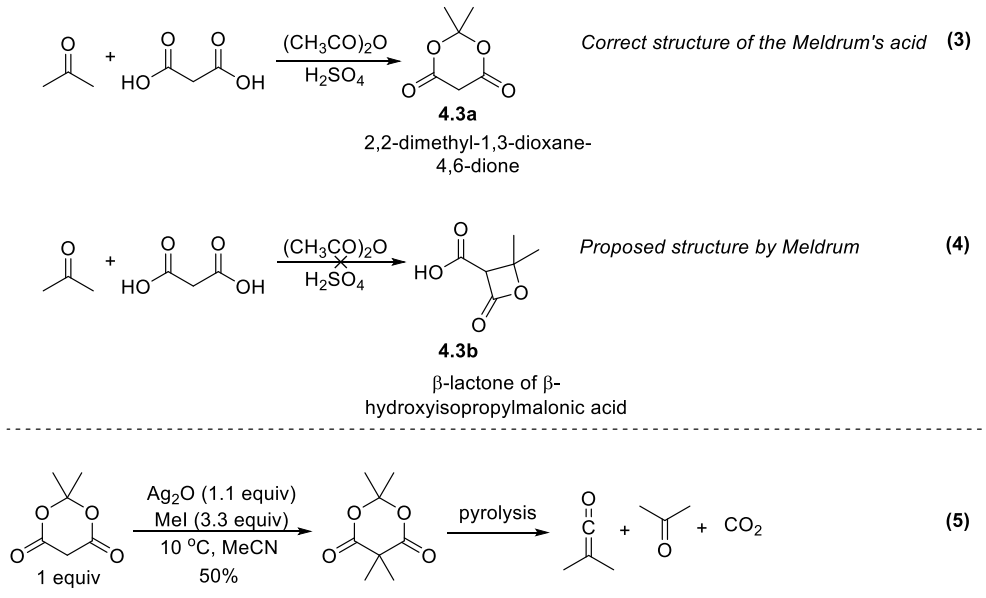


Scheme 4.2 Addition-elimination pathway of S_NAr reactions

Among all the nucleophilic additions to fluoroarenes, we were particularly interested in methods which lead to C–C bond formations.[9a] The addition of Meldrum's acid as a nucleophile has not been reported in literature, and this was surprising given that the addition would allow a facile access to previously inaccessible α-perfluoroarylacetic acid derivatives. In that vein, we sought to develop a method to add Meldrum's acid to perfluoroarenes.

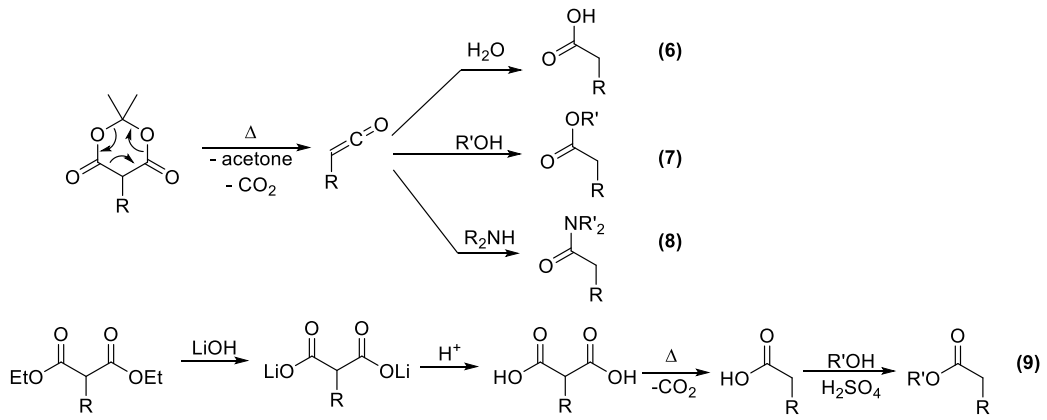
Meldrum's acid was initially discovered in 1908 by Andrew Norman Meldrum as a condensation product between acetone and malonic acid (Scheme 4.3) .[88] The product was titrated as a monobasic acid in an aqueous solution and lost carbon dioxide upon heating. Given the evidence, he reasonably claimed that "there can hardly be a doubt" that the compound was the carboxylic acid[88] and the structure of the new compound was assigned as the β-lactone of β-hydroxyisopropylmalonic acid (**4.3b**, 2,2-dimethyl-4-oxooxetane-3-carboxylic acid). However, despite Meldrum's confidence in his structural assignment, he was wrong. This misidentification remained so for the next 40 years until it was correctly assigned by Davidson (**4.3a**).[89] If the carboxylic acid is present in the structure it would be feasible to esterify. However, treatment of the Meldrum's product with alcohol and an acid catalyst resulted in scission to acetone and diethyl malonate as opposed to an esterification, which caused Davidson to question the carboxylic acid functionality. Furthermore, Davidson reacted the silver salt of Meldrum's acid with MeI and failed to observe any ester in the product and the only reaction reported being its

pyrolysis to acetone, carbon dioxide and dimethylketene (eq 5). The occurrence of dimethylketene among the products of pyrolysis of the dimethyl derivative suggested that the substance is actually related to dimethylmalonic acid and, therefore, that the methylene group contained in malonic acid is still present in Meldrum's acid. Davidson, concluded that the 6-membered O,O-acetal, which we know now, is the correct structure of Meldrum's acid.



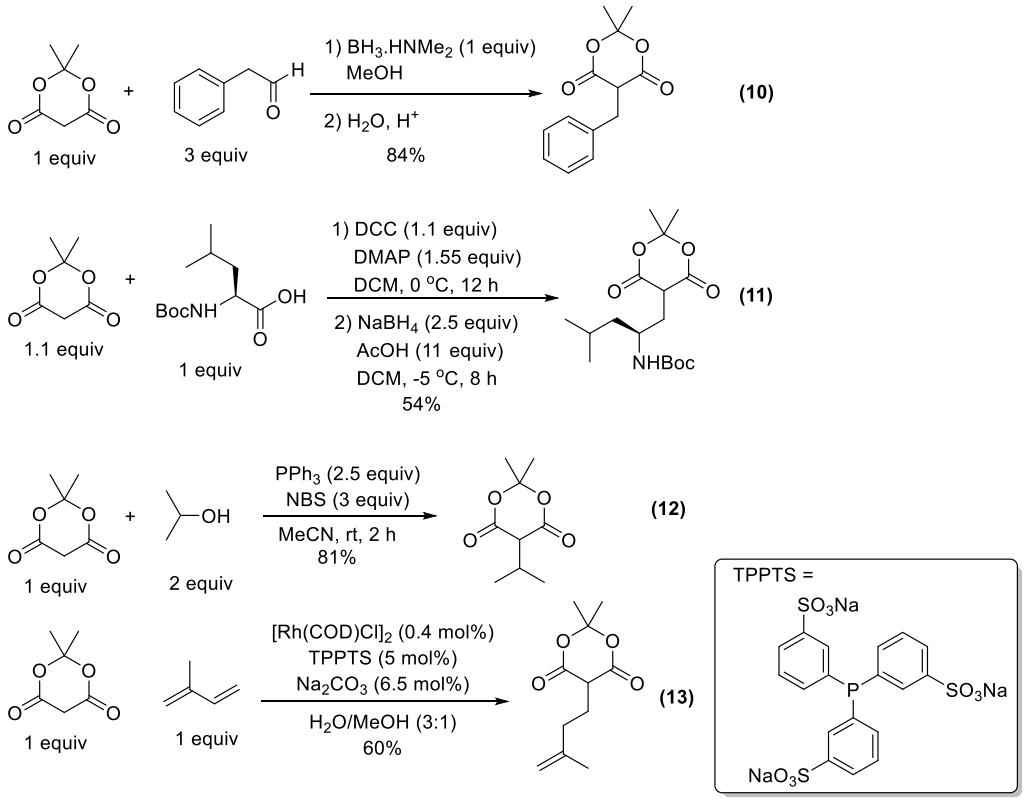
Scheme 4.3 Correct and incorrectly assigned structures of Meldrum's acid

Even though, both Meldrum's acid (MA) and its cousin, diethyl malonate share significant structural similarities, i.e., the 1,3-dicarbonyl motif, Meldrum's acid possesses an anomalous acidity[90] (p*K*a = 7.3 in DMSO)[91] compared to its malonate cousin (diethyl malonate, p*K*a = 16.4 in DMSO)[90-91] and therefore has a long and rich history as an activated nucleophile. Meldrum's acid, and its derivatives, can be hydrolyzed easily under acidic conditions allowing facile elaboration which is not possible with malonates. For instance, derivatization of MA can be done *via* a ketene intermediate in a single step with variety of nucleophiles (Scheme 4.4, eq 6-8) in contrast to multistep sequence needed for malonates (eq 9).



Scheme 4.4 Single step derivatization of MA compared to the lengthy sequence needed for malonate esters

Numerous strategies for the selective alkylation of MA have been well developed. Those include reductive alkylation of aldehydes (Scheme 4.5, eq 10),[92] coupling and reduction of carboxylic acids (eq 11),[93] substitution of Mitsunubu reagents (eq 12), prenylation with cationic metal allyls (eq 13), addition to Michael acceptors,[94] and substitution of alkyl halides[95] etc. A few selected examples are shown below.



Scheme 4.5 Selective mono-alkylation of MA

In contrast to the number of strategies for alkylation of MA, the corresponding arylation is far less developed, and yet represents a valuable class of reactions. Monoarylated MA at the α-position would provide access to α-arylacetic acid derivatives which are prevalent in many biologically relevant compounds (Figure 4.1).[96] Chen and Stang[97] have shown that diaryliodonium salts can be utilized (Scheme 4.6, eq 14) as the arylation reagent for such transformations. Furthermore, Pinhey[98] has shown that aryl-lead triacetates can undergo facile coupling with α-substituted Meldrum's acids (eq 15) in good yields.

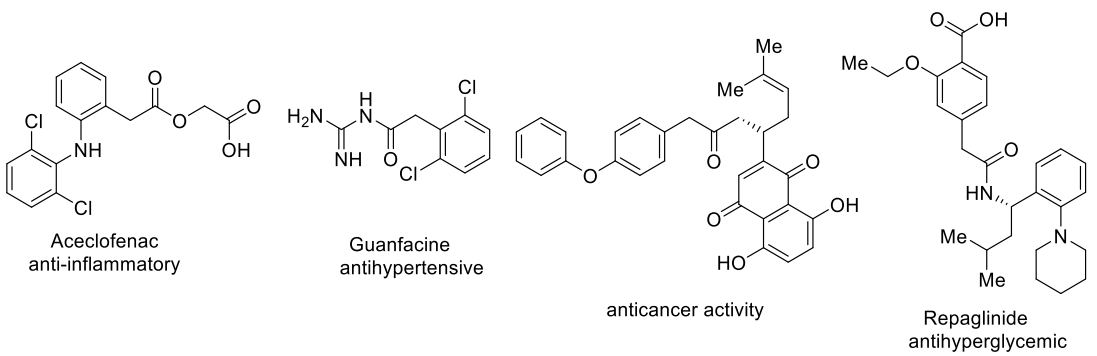
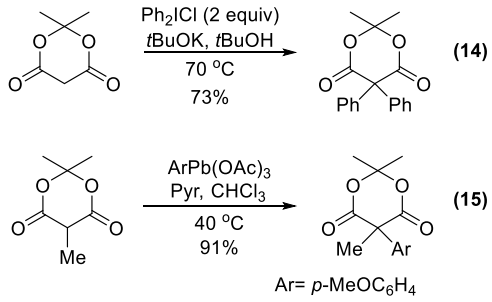


Figure 4.1 Biologically important α-arylacetic acid derivatives



Scheme 4.6 Arylation strategies for MA

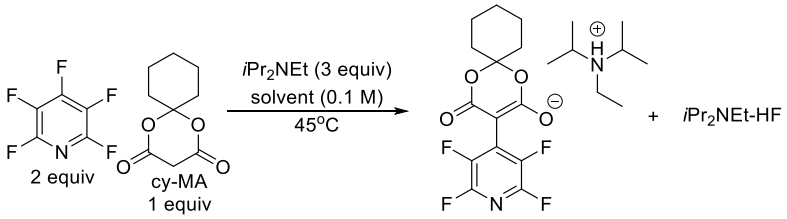
However, these reactions always lead to the fully quaternerized products. Thus, methods that allow for the selective monoarylation of MA are needed to be able to access MA adducts which possesses a tertiary center, or alternatively, an unsymmetric quaternerized center.

As a part of our C–F functionalization program, we are interested in increasing the pool of fluorinated arene building blocks as well as methods for their further elaboration. As described above, perfluoroarenes are known to readily undergo S_NAr reactons.[99] However, addition of MA to perfluoroarenes have never been reported. Therefore, we decided to formulate a method for direct per(poly)fluoroarylation of MA. Given the versatility of MA and its adducts,[100] we anticipated that the products would be highly useful for making advanced polyfluorinated arenes and heteroarenes.

4.2 Development of the per- and polyfluoroarylation of MA

We commenced our investigation using pentafluoropyridine and 1,5-dioxaspiro[5.5]undecane-2,4-dione (cy-MA) along with *i*Pr$_2$NEt as the base in MeCN (Table 4.1). In this analog of MA, the normal [5.5] dimethyl group has been replaced with a cyclohexyl group. As a consequence, cy-MA is more soluble[100a] in most organic solvents and possesses a greater hydrolytic stability[101] than simple Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) which is more susceptible to hydrolysis over time. On our first attempt to couple cy-MA and pentafluoropyridine, we were pleased to observe a clean conversion to the product (entry 1). During the solvent screening several trends became clear. First, polar aprotic solvents worked well (entries 1-3) while protic- (entry 4), halogenated- (entry 5), aromatic- (entry 6) and ethereal-solvents (entry 7) were found to be inferior. Finally, MeCN was chosen as the solvent to move forward because of its comparatively greater volatility than other polar aprotic solvents facilitated isolation.

Table 4.1 Solvent screen for the perfluoroarylation of MA

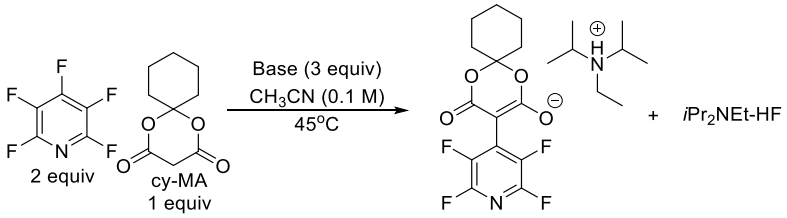


entry	solvent	time (h)	% conv.[a]
1	MeCN	2, 5	93/100
2	DMSO	2, 5	100/100
3	DMA	2, 5	100/100
4	IPA	2, 5	3/6
5	DCM	2, 5	17/28
6	Tol	2, 5	ND[b]
7	THF	2, 5	13/23

[a] Conversions determined by ^{19}F NMR. [b] ND = not detected.

A base is needed to deprotonate the acidic αC–H of cy-MA to generate the corresponding nucleophile from the pro-nucleophile which can then attack the fluoroarene. Therefore, a base screening was performed using Et_3N as an organic base and K_2CO_3 as an inorganic base (Table 4.2). Even though, triethylamine gave similar conversions to the standard reaction (entry 2), it also yielded an undesired *N*-arylated side-product[102] and K_2CO_3 gave a very sluggish reaction presumably due to heterogeneity of the reaction. This led us to use *i*Pr_2NEt as the base for further optimizations.

Table 4.2 Base screen for the reaction

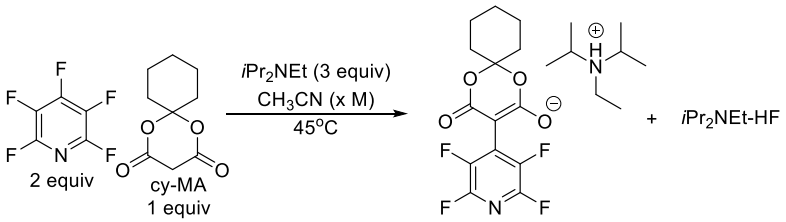


entry	base	time (h)	% conv.[a]
1	*i*Pr_2NEt	2, 5	93, 100
2	Et_3N	2, 5	87, 100
3	K_2CO_3	2, 5	10, 15

[a] Conversions determined by 19F NMR

Finally, the effect of concentration was briefly examined in hopes of concentrating the reaction without sacrificing the cleanliness (Table 4.3). Generally, when the concentration was increased, the reaction rate went up as a consequence of more productive collisions. Indeed, the rate of the reaction displayed a concentration dependency, and thus the reactions were run at 1 M concentration in order to shorten the reaction times. Higher concentrations were challenging to work with, as they approached the limit of homogeneity.

Table 4.3 Concentration study of the reaction



entry	concentration	time	% conv.[a]
1	0.05 M in MeCN	4.5 h	45
2	0.1 M in MeCN	4.5 h	73
3	0.2 M in MeCN	4.5 h	100
4	1.0 M in MeCN	20 min	100

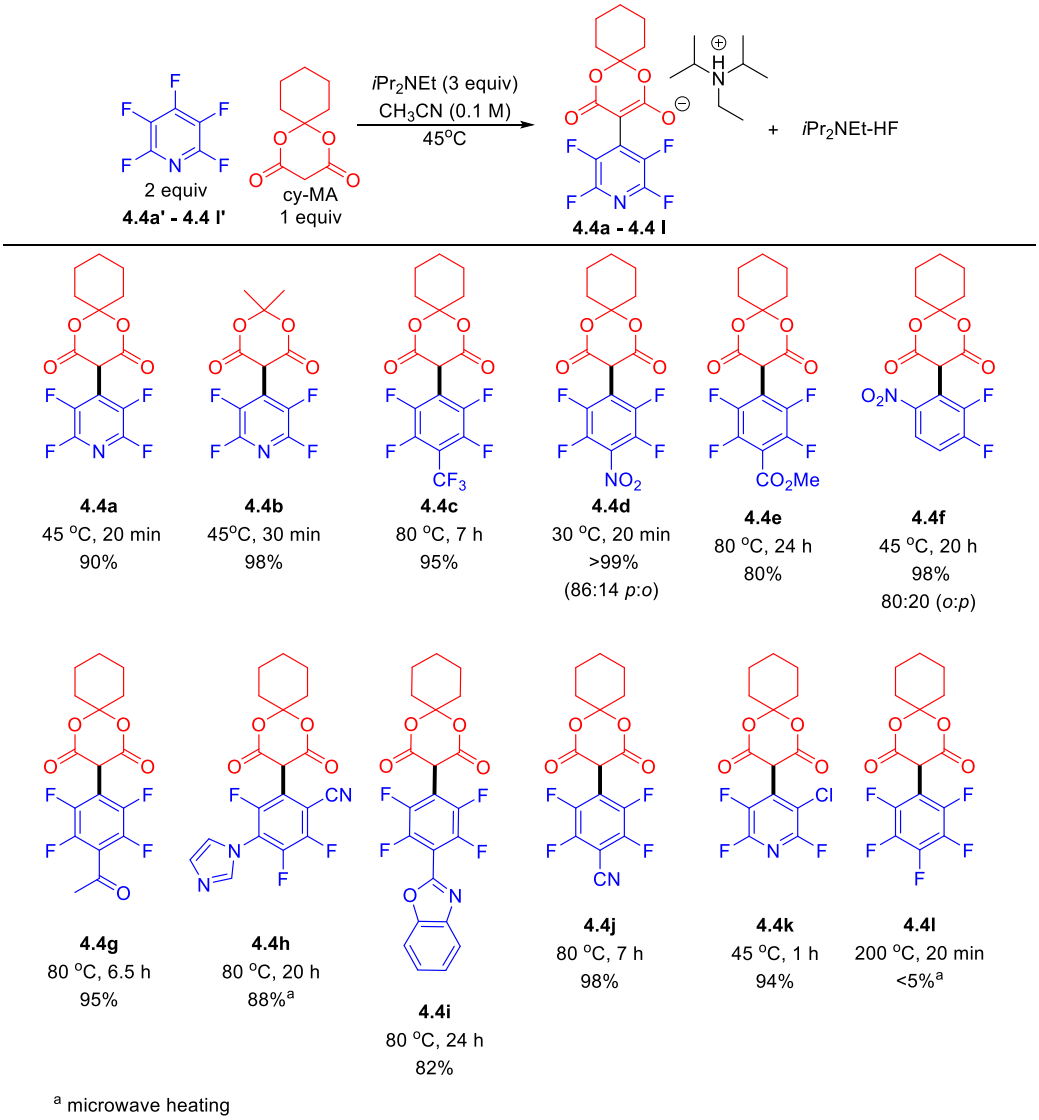
[a] Conversions determined by 19F NMR

Having figured out conditions to rapidly obtain the desired products cleanly, we next sought to develop workup conditions that would allow us to isolate the *i*Pr$_2$NEt-MA adduct as a salt. When the reaction was completed the crude contained left over perfluoroarene, *i*Pr$_2$NEt and *i*Pr$_2$NEt-HF salt along with the desired product. In the case of volatile perfluoroaryl starting materials, excess arylfluoride and *i*Pr$_2$NEt were removed by evaporation and the *i*Pr$_2$NEt-HF salt was removed simply by taking the crude product in to DCM and washing with water. For non-volatile perfluoroarenes the remaining starting material was removed by a trituration with pentane after performing the same evaporation and water wash as stated above (see experimental section for further details of the workup). The workups allow rapid isolation in high yield with no need for column chromatography which should facilitate its implementation on a larger scale.

Then, we looked at the scope of the reaction (Table 4.4). Perfluoroarylation of MA was compatible with nitro substituents (**4.4d** and **f**), ketones (**4.4g**), nitriles (**4.4h** and **4.4j**), and esters (**4.4e**) as well as trifluoromethyl groups (**4.4c**). Among the heteroaromatics tested, the reaction worked well for pyridines (**4.4a-b** and **4.4k**) and some fused heteroarenes (**4.4h-i**). When used as starting materials, nitroarenes gave regioisomeric mixtures of products (**4.4d** and **4.4f**).

Consistent with the S_NAr mechanism selective addition to the C-4 of 3-chloro-2,4,5-trifluoropyridine was observed leaving C–Cl as a handle for further functionalizations yielding the product **4.4k**. As mentioned previously, there are no MA arylation methods that can generate the tertiary MA adducts, it is therefore, remarkable that the reaction can selectively give the monoarylated product with no overarylation. This makes the methods distinct from existing arylations of MA.[97-98] Possible reasons for this observation will be discussed below, when we describe our attempts to alkylate these adducts.

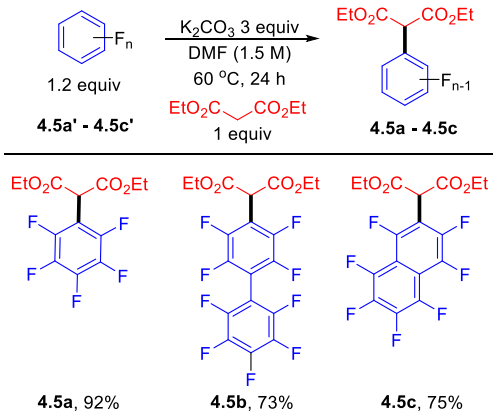
Table 4.4 Scope of per- and polyfluoroarylation of MA



[a] microwave heating

Unfortunately, we were not able to engage unactivated perfluoroarenes in the reaction. For instance, the reaction did not work for simple hexafluorobenzene even at elevated temperatures (200 °C) where it remained mostly unchanged (**4.4l**). We speculated that the lack of reactivity is due to an extreme reaction barrier, which may be possible to overcome by increasing the reactivity of the nucleophile. To accomplish this, we turned to the corresponding malonate ester which is significantly more basic (diethyl malonate p*K*a = 16.4 in DMSO)[103] and consequently more nucleophilic. As expected diethyl malonate engaged in the reaction with unactivated perfluoroarenes such as hexafluorobenzene, decafluorobiphenyl, and octafluoronapthalene yielding a single regioisomer, even at temperatures < 80 °C (Table 4.5). Even though, we prefer to obtain products between MA and perfluoroarenes due to its easier elaboration after the reaction, ultimately this does provide access to a similar 1,3-diester motif by switching the nucleophile to diethyl malonate.

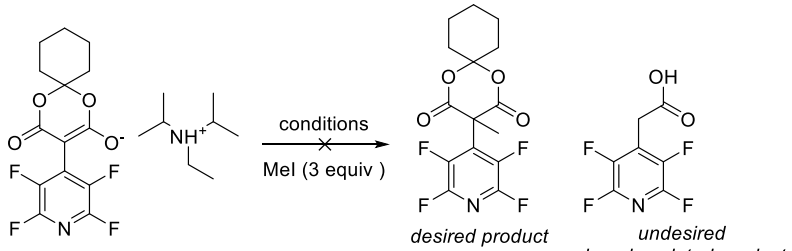
Table 4.5 Scope of the reaction between diethylmalonate and unactivated perfluoroarenes



After obtaining tertiary centers by substituting the cy-MA with variety of perfluoroarenes we sought to fully quaternerize the remaining activated methine *via* alkylation. For this, we attempted to use standard reaction conditions which facilitate alkylation[104] and those conditions are summarized in Table 4.6. However, rather than seeing the desired alkylated product we observed the decarboxylated product along with several other byproducts at high temperatures.

The lack of alkylation could be due to either steric or electronic inhibition (or alternatively a combination of both). Our suspicion was that the additional stabilization of the cy-MA carbanion by the perfluoroarene significantly reduced the nucleophilicity of the carbanion and is more responsible for the diminished alkylation.[105]

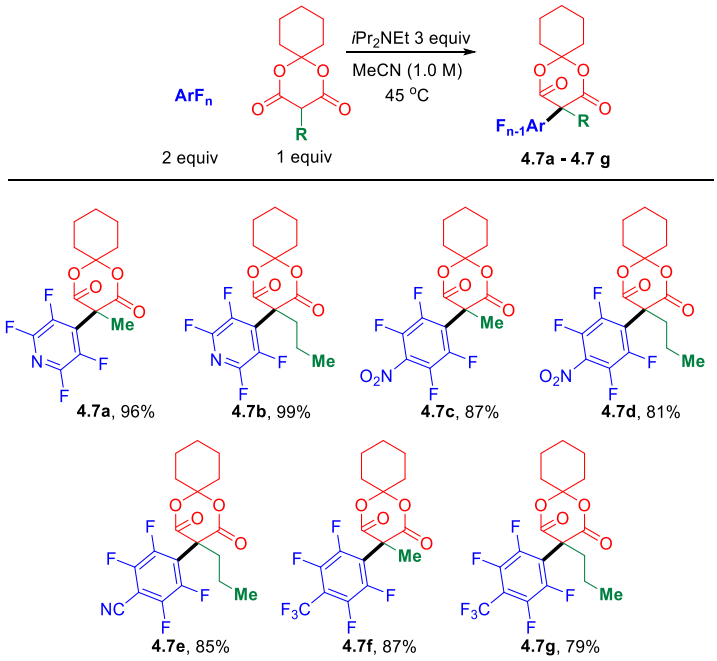
Table 4.6 Failed direct alkylation reaction of the adducts



entry	conditions	time (h)	conv %
1	DMF (0.1 M), K_2CO_3 (3 equiv), 30 °C	3	ND[a]
2	DMF (0.1 M), K_2CO_3 (3 equiv), 45 °C	17	30% conv to the decarboxylated product
3	DMF (0.1 M), K_2CO_3 (3 equiv), 80 °C	15	Decarboxylated product and several byproducts formed
4	acetone (0.1 M), K_2CO_3 (3 equiv), 30 °C	3	ND[a]
5	acetone (0.1 M), K_2CO_3 (3 equiv), 45 °C	17	35% conv to the decarboxylated product
6	acetone (0.1 M), K_2CO_3 (3 equiv), 80 °C	15	Decarboxylated product and several byproducts formed

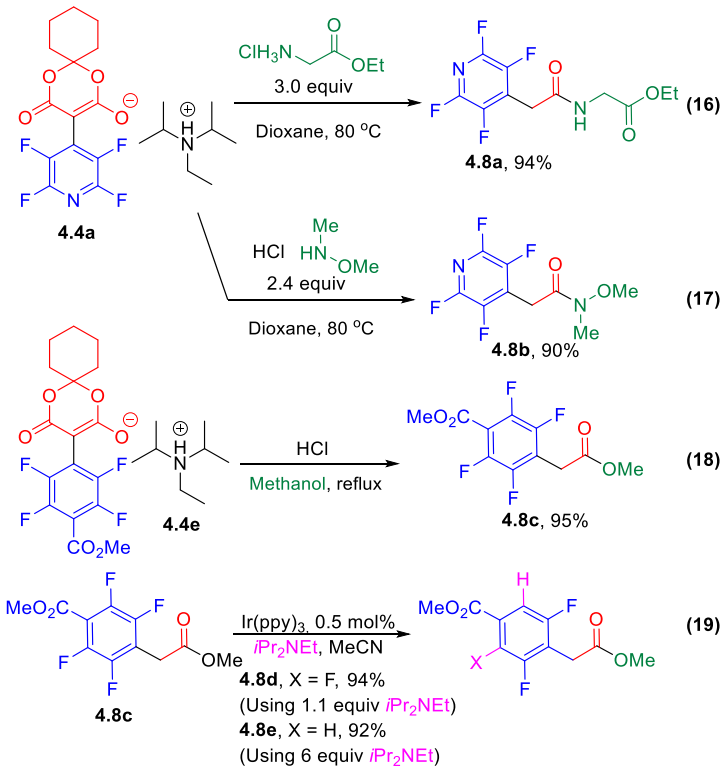
Nonetheless, since we did not have any luck with the standard alkylations we were forced to reevaluate our strategy. At this point we decided to alkylate cy-MA and appraise the likelihood to add that to a perfluoroarene. If successful, this will lead to the exact same quaternarized product we desired. We were excited to find the additions took place smoothly with no alterations from the initial conditions despite the fact that the reaction forms a quaternary center. To some extent, this supports the idea that the inability to alkylate the perfluoroarylated MA adducts is due to electronic reasons rather than steric issues, though admittedly the two transition states are not the same. To demonstrate the reactivity we carried out alkylations of fluoroarenes with both methylated and propylated cy-MA (Table 4.7).

Table 4.7 Addition of α-Alkylated MAs to Perfluoroarenes



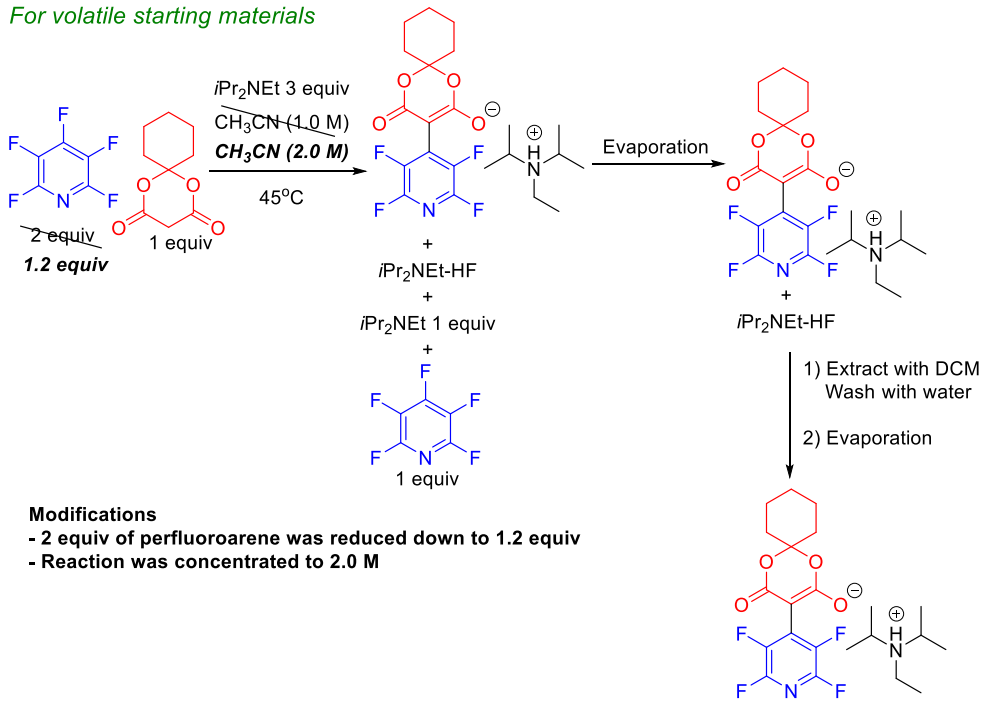
Addition of MA to perfluoroarenes was developed to use the products as per(poly)fluoroaryl building blocks. Therefore, we sought to demonstrate the utility of the cy-MA adducts as highly functionalizable starting materials. It is known that MA adducts can undergo facile hydrolysis and nucleophilic addition especially, under acidic conditions.[100b, 106] Relatively facile ring opening and decarboxylation occur when the adducts are exposed to a nucleophile under conditions that protonate the enolate (i.e., decarboxylation is observed at rt overnight). In contrast, the typical decarboxylation of 1,3-diacids occur at temperatures well over 100 °C,[107] we found that the decarboxylation is significantly accelerated in perfluoroarylated MA adducts such that it takes place readily at methanolic reflux and even at room temperature albeit at lower rates (see experimental section for details). For demonstration purposes glycine ethyl ester, Weinreb amine and methanol were chosen as nucleophiles. Glycine ethyl ester underwent smooth acylation to afford the amide product (Scheme 4.7, eq 16). The Weinreb amide, which is a useful synthetic intermediate for the formation of ketones[108] by addition of organometallics, was

also formed by the addition of its amine-HCl salt along with gentle heating (eq 17) in dioxane. Later, it was found that dioxane can be substituted with more volatile MeCN which allowed us to easily remove the solvent during the workup as opposed to multiple water washes to remove dioxane. Furthermore, the reaction was cleaner in MeCN than in dioxane and also achieved slightly higher yields.[36b] The addition product between methyl perfluorobenzoate and cy-MA was methanolized under acidic conditions to form the dimethyl ester **4.8c**. The product ester was then subjected to the photo-HDF[16a] reaction in hopes of reducing the fluorine content to obtain the corresponding partially fluorinated molecules. By simply controlling the amount of amine reductant we were able to access both mono- and di- reduction products cleanly (eq 19). These reactions display the strength of the synergistic use of S_NAr and photocatalysis as a facile and a rapid way to access functionalized, partially fluorinated arenes which are nearly impossible to obtain using any other existing technology.



Scheme 4.7 Further elaboration of MA adducts

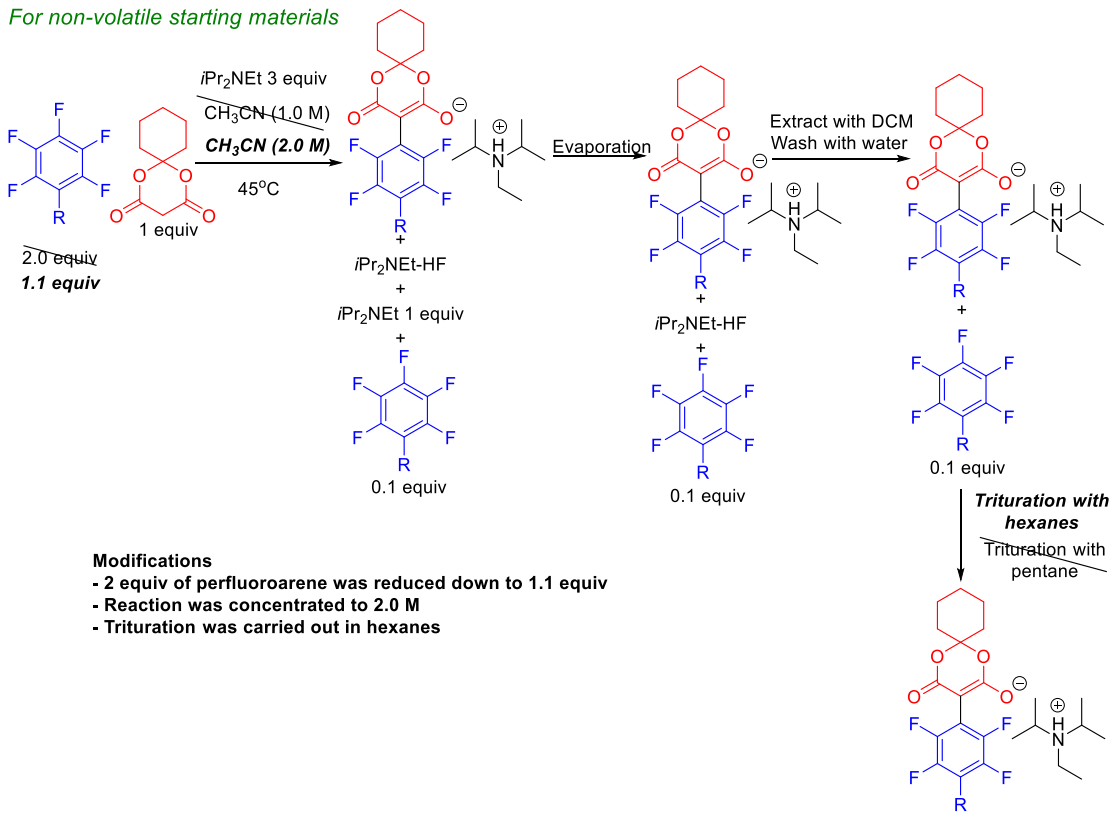
We envisioned the α-polyfluoroarylated molecules as a versatile class of molecules that could be utilized for the elaboration and incorporation of polyfluoroarenes into other molecules of interest. Therefore, we turned our attention to further optimize our method to make it scalable. In this regard, we first attempted to lower the relative amount of perfluoroarene from 2 equivalents to 1.2 equivalents and increased the reaction concentration from 1.0 M to 2.0 M in MeCN (Scheme 4.8).



Scheme 4.8 Development of an isolation method for MA adducts when volatile perfluoroarenes are used

When nonvolatile perfluoroarenes are used at the end of the reaction, the removal of the excess starting material was a struggle with no column chromatography. Knowing the highly ionic nature of the final adduct salt and the extreme nonpolar nature of the fluoroarene, we turned our attention to selectively extract the excess fluoroarene into a nonpolar solvent and precipitate the product salt as a solid. For this, we designed a trituration method (see experimental section

for details) to selectively precipitate the product with extraction of the perfluoroarenes to pentane. The crude product was dissolved in a minimal amount of DCM and pentane was added with vigorous stirring. During the process, the desired product precipitated as a solid leaving nonvolatile, nonpolar starting materials in the pentane layer. However, later we were able to substitute pentane with hexanes which is a cheaper alternative (Scheme 4.9). These changes allowed us to design a more economical scale up procedure for commercialization of per- and polyfluoroarylated MA adducts. All the MA adducts were scaled up (some of them were in 25-50 g scale) using the modified methods without hurting the yields or purities. Commercialized adducts are now available through Aspira Scientific[109] and Sigma-Aldrich.[110]



Scheme 4.9 Development of an isolation method for MA adducts when nonvolatile perfluoroarenes are used

4.3 Summary of the per- and polyfluoroarylation of MA

In summary, during this project we have developed reaction conditions that facilitate the per- and polyfluoroarylation of Medrum's acid to generate a whole new class of synthetically versatile highly fluorinated building blocks. By taking advantage of the reduced nucleophilicity of the products this reaction allows, for the first time, the selective monoarylation of MA to give access to tertiary centers. We also demonstrated the ability of quaternarizing the α-carbon by reversing the order of events. Given the prevalence of partially fluorinated arenes in disparate fields, we hoped this simple, cheap and scalable method would serve the needs of the community by providing access to one type of fluoroarene building block.

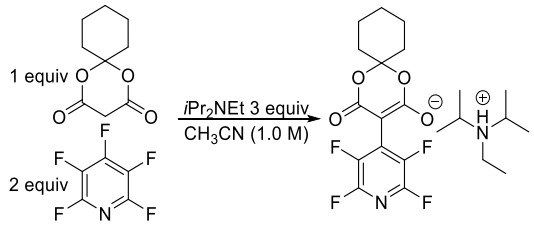
4.3 Experimental section

General Experimental

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Acetonitrile (MeCN) was dried over molecular sieves. Photocatalyst *tris*-(2-phenyl pyridinato-C^2, *N*)iridium(III) , 99% (purity), ($Ir(ppy)_3$) was obtained from Sigma-Aldrich. Methyl-2,3,4,5,6-pentafluorobenzoate (**4.4e'**, ref- Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002.), 2-(perfluorophenyl)benzo[*d*]oxazole (**4.4i'**, ref- Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002.), 2,3,5,6-tetrafluoro-4-(1H-imidazol-1-yl)benzonitrile (**4.4h'**, ref- Fujii, S.; Maki, Y.; Kimoto, H. *J. Fluorine Chem.* **1989**, 43, 131.) and cyclohexyl-Meldrum's acid (cy-MA, ref- Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chem. Sci*. **2012**, 3, 121.), were synthesized according to literature procedures. NMR spectra were obtained on 400 MHz spectrometers. ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^1H, ^{13}C). Melting points were reported uncorrected. HRMS data were obtained using LTQ (linear trap quadrupole) Orbitrap XL mass spectrometer. Isolations were carried out using an automated chromatography

system using normal phase silica (4 g, 12 g 24 g, or 40 g) with product detection at 254, 280 nm and using an evaporative light scattering detector (ELSD). Substrate syntheses reactions were monitored by thin layer chromatography (TLC), with UV254, glass backed, 250 µm, and were visualized with ultraviolet light or potassium permanganate.

General Procedure A for the fluoroarylation of unsubstituted-MA.



For monitoring purposes, these reactions were carried out in NMR tubes and monitored *via* ^{19}F NMR. An NMR tube was charged with cyclohexyl-Meldrum's acid (1 equiv), CH_3CN (1.0 M), followed by *i*Pr_2NEt (3 equiv) and fluorinated starting material **4.4a'- 4.4l'** (1.2 or 2 equiv) was added and a sealed glass capillary containing C_6D_6 was placed in NMR tube for locking purposes. Then the NMR tube was capped and placed in a sand bath and maintained at indicated temperature (30, 45 or 80 ºC). The NMR tube was occasionally removed from the sand bath and the reaction progress checked by ^{19}F NMR.

General workup method B for the isolation of the fluoroarylated-MA adduct (for volatile starting materials).

After reaction completion as judged by ^{19}F NMR, CH_3CN and excess volatile starting material were removed *via* rotavap, and the residue was dissolved in DCM (2 mL), and washed with deionized water (2 mL) which selectively removed the *i*Pr_2NEt-HF salt. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield the title compound.

General workup method C for the isolation of the fluoroarylated-MA adduct (for non-volatile per- and polyfluoroarene starting materials).

In the case of less volatile fluoroarene starting materials, purification of the crude material was performed by using the following purification method. After reaction completion as judged by ^{19}F NMR, CH_3CN was removed *via* rotavap and the residue was dissolved in DCM (2 mL) and washed with deionized water (2 mL) to remove *i*Pr_2NEt-HF salt. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was further purified *via* trituration. In a borosilicate test tube the sample was dissolved in minimal amount (~0.5 mL) of ethyl acetate and pentane (~5.0 mL) was added with vigorous stirring which resulted in the precipitation of the product and selective dissolution of the excess fluoroarene starting material (typically 1.2 equiv. used) and the ethyl acetate into the pentane layer, leaving behind the product as a solid. The product was then separated by decantation of the pentane layer which contained the excess starting material. Finally, the product was placed in vacuum to remove any leftover pentane to yield the title compound.

General Procedure D for the fluoroarylation of diethyl malonate.

These reactions were carried out in 0.5-2.0 mL microwave vials. A microwave vial was charged with diethyl malonate (1 equiv), DMF (1.6 M), fluorinated starting material (1.2 equiv), K_2CO_3 **(**3.0 equiv) and then a magnetic stir bar was added. The microwave vial was placed in a sand bath and maintained at 60 °C. The reaction was monitored by ^{19}F NMR by pulling out small aliquots using a syringe and a needle. After the completion of the reaction, the residue was dissolved in DCM (~ 4 × the vol of DMF) and washed with deionized water (3 × 5 mL) to remove K_2CO_3 and DMF. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by normal phase chromatography with hexanes and ethyl acetate.

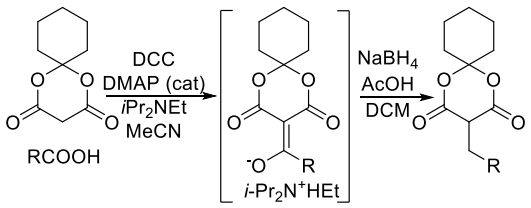
General Procedure E for the fluoroarylation of substituted-MA.

For the monitoring purposes, these reactions were carried out in NMR tubes and monitored *via* ^{19}F NMR. An NMR tube was charged with alkylated-Meldrum's acid (1 equiv), CH_3CN (1.0 M), fluorinated starting material (2 equiv) and *i*Pr_2NEt **(**3 equiv) were added and sealed glass capillary containing C_6D_6 was placed in NMR tube for locking purposes. Then the NMR tube was placed in a sand bath and maintained at appropriate temperature (30, 45 or 80 ^oC). The reaction was monitored by ^{19}F NMR.

General Procedure F for the photocatalytic hydrodefluorination reaction.

An NMR tube capped with NMR septum (Ace glass, part no. 9096-25) was charged *tris*-(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (1 mL of a 0.5 mM solution in MeCN). Fluorinated starting material **4.8c** (1.0 equiv), *i*Pr_2NEt (1.1 or 6.0 equiv), and a sealed glass capillary containing C_6D_6 for locking purposes were added before degassing. Then the reaction was degassed through the septum *via* Ar bubbling for 5-10 min at 0 ^oC (to avoid evaporation of *i*Pr_2NEt. The NMR tube was placed in a light bath and the lower portion of the tube was submerged under the water bath which was maintained at 45 ^oC. The reaction was periodically monitored by ^{19}F NMR. After the reaction completion, CH_3CN was removed *via* rotavap and the residue was treated with deionized water (2 mL) and extracted with EtOAc (5 x 1 mL). The combined organic portions were dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo,* and purified by normal phase chromatography.

General procedure G for the alkylation of MA.



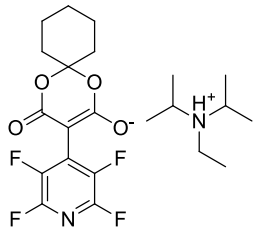
These reactions were carried out in one pot-2 step procedure. In a 100 mL round-bottomed flask, the corresponding carboxylic acid (1.0 equiv) and MeCN (0.2 M) were added, followed by

cyclohexyl-Meldrum's acid (1.1 equiv). To the stirring mixture, DMAP (4-dimethylaminopyridine) (0.1 equiv) was added, followed by the dropwise addition of *i*Pr_2NEt (2.15 eq). Then, DCC (*N*,*N*'-dicyclohexylcarbodiimide) (1.1 equiv) was added and the reaction was stirred at room temperature for 14 h. Then MeCN was evaporated *in vacuo,* and the crude material was taken onto the next step without further purification. In the second step, the crude material was dissolved in DCM (0.2 M) was cooled to 0 °C and acetic acid (10 equiv) was added followed by the portion-wise addition of $NaBH_4$ (2.5 equiv). The reaction mixture was allowed to warm to room temperature and stirred overnight. Then the reaction was diluted with water (20 mL), acidified with 1 M HCl. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resultant crude residue was purified by automated flash chromatography to give the product.

General procedure H for the aminolysis reaction of the fluoroarylated-MA adduct

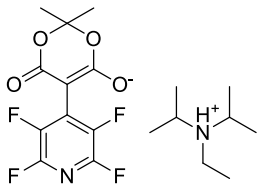
For the monitoring purposes, these reactions were carried out in NMR tubes and monitored *via* ^{19}F NMR. An NMR tube was charged with **4.4a** (1.0 equiv), the amine-HCl salt (2.4 or 3.0 equiv), and dioxane (0.1 M). A sealed glass capillary containing C_6D_6 was placed in NMR tube for locking purposes. Then the NMR tube was placed in a sand bath and maintained at 80 °C. The reaction was periodically monitored by ^{19}F NMR. After the completion of the reaction the residue was dissolved in DCM (2 mL) and washed with deionized water (3 × 5 mL) to remove dioxane. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the title compound.

Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4a)



The general procedure **A** was followed using pentafluoropyridine (220 µL, 2.0 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid (184 mg, 1.0 mmol, 1.0 equiv), *i*Pr_2NEt (522 µL, 3.0 mmol, 3.0 equiv) and CH_3CN (1.0 mL). After the completion of the reaction the workup method B was used to isolate **4.4a** in 90% yield as a light yellow solid (416.0 mg, 0.9 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.5 – -96.8 (m, 2F), -138.6 – -138.9 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 – 3.50 (m, 2H), 3.04 (qd, *J* = 7.4, 4.0 Hz, 2H), 2.08 – 1.98 (m, 4H), 1.65 (p, *J* = 6.6 Hz, 4H), 1.50 – 1.32 (m, 17H). ^{13}C (101 MHz, $CDCl_3$) δ 164.2, 144.8 – 141.9 (m, overlapped), 142.1 – 138.5 (m, overlapped), 131.9 (ddd, *J* = 20.1, 16.8, 3.5 Hz), 103.1, 67.7, 54.4, 42.7, 34.8, 25.0, 22.7, 18.4, 17.0, 12.4. mp 138-140 °C. FT-IR(neat) cm^{-1} 2935, 1605, 1254, 1368, 1466. HRMS (ESI) calcd. $C_{14}H_{10}F_4NO_4^-$ 332.0551 observed 332.0532.

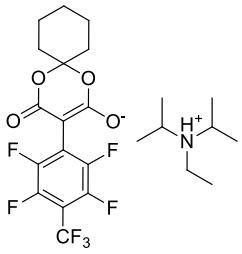
Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 2,2-dimethyl-4-oxo-5-(perfluoropyridin-4-yl)-4H-1,3-dioxin-6-olate (4.4b)



The general procedure **A** was followed using pentafluoropyridine (110 µL, 1.0 mmol, 2.0 equiv), Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (72.0 mg, 0.5 mmol, 1.0 equiv), *i*Pr_2NEt (261 µL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was used to isolate **4.4b** in 98% yield as a white solid (207.0 mg, 0.49 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -95.6 – -95.9 (m, 2F), -138.2 – -138.4 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (hept, *J* = 13.0, 6.5 Hz, 2H), 3.04 – 2.90 (m, 2H), 1.60 (s, 6H), 1.31 – 1.21 (m, 15H). ^{13}C (101 MHz, $CDCl_3$) δ 164.5, 144.9 – 141.9 (m, overlapped), 142.0 – 138.9 (m, overlapped), 131.8 (tt, *J* = 16.6, 3.4 Hz), 102.5, 67.6 (d, *J* = 4.6 Hz), 54.4, 42.7, 26.0, 18.4, 17.1, 12.4. mp 102-104 °C.

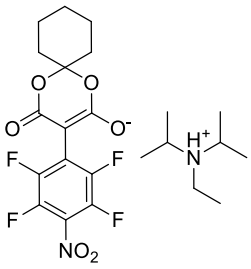
FT-IR(neat) cm^{-1} 2992, 2958, 1600, 1266. HRMS (ESI) calcd. $C_{11}H_6F_4NO_4^-$ 292.0238 observed 292.0217.

Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4c)



The general procedure **A** was followed using octafluorotoluene (283 µL, 2.0 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid (184.0 mg, 1.0 mmol, 1.0 equiv), *i*Pr_2NEt (522 µL, 3.0 mmol, 3.0 equiv), and CH_3CN (1.0 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4c** in 95% yield as a sticky white solid (502.7 mg, 0.95 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.0 (t, *J* = 21.6, 6.8 Hz, 3F), -135.2 – -135.4 (m, 2F), -144.7 – -145.1 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$) δ 3.50 – 3.35 (m, 2H), 2.97 – 2.86 (m, 2H), 2.00 – 1.76 (m, 4H), 1.50 (p, *J* = 5.9 Hz, 4H), 1.38 – 1.10 (m, 17H). ^{13}C (101 MHz, $CDCl_3$) δ 164.4, 146.8 – 143.7 (m), 143.7 (dd, *J* = 255.7, 17.5 Hz), 122.6 (d, *J* = 19.5 Hz), 121.2 (d, *J* = 234.0 Hz), 105.0 (qt, *J* = 33.8, 12.8 Hz), 102.7, 66.4, 54.1, 42.4, 34.5, 24.8, 22.4, 18.1, 16.7, 12.1. mp 100-101 °C. FT-IR(neat) cm^{-1} 2936, 2706, 1593, 1286. HRMS (ESI) calcd. $C_{16}H_{10}F_7O_4^-$ 399.0473 observed 399.0448.

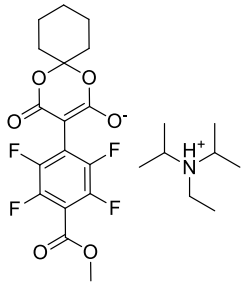
Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4d)



The general procedure **A** was followed using pentafluoronitrobenzene (66.7 µL, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid (92.0 mg, 0.5 mmol, 1.0 equiv), *i*Pr_2NEt (260 µL, 1.5 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4d** in >99% yield as a brown sticky solid (253 mg, 0.5 mmol). The isolated product contained *para* and *ortho* substituted compounds in 7.1:1 ratio as

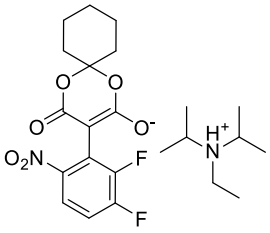
determined by the ^{19}F NMR of the isolated material. ^{19}F NMR of the mixture (376 MHz, $CDCl_3$) δ -132.2 (minor, dd, *J* = 23.6, 9.5 Hz, 1F), -133.3 – -133.5 (major, m, 2F), -149.9 (minor, ddd, *J* = 21.7, 9.3, 4.1 Hz, 1F), -150.5 (major, td, *J* = 15.4, 14.7, 10.0 Hz, 2F), -152.1 – -152.4 (minor, m, 1F), -159.1 (minor, t, *J* = 21.2 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (h, *J* = 10.2, 6.6, 3.7 Hz, 2H), 3.10 – 2.99 (m, 2H), 2.08 – 2.00 (m, 4H), 1.66 (p, *J* = 6.7 Hz, 4H), 1.52 – 1.34 (m, 17H). ^{13}C of the mixture (101 MHz, $CDCl_3$) δ 164.6 , 164.2 , 146.5 (d, *J* = 6.3 Hz), 144.9 (ddd, *J* = 243.9, 10.5, 7.0 Hz), 142.7 – 139.6 (m), 140.2 (dd, *J* = 258.3, 18.8 Hz), 135.7 – 135.3 (m), 126.8 (t, *J* = 12.8 Hz), 123.4 (t, *J* = 18.5 Hz), 118.7 (dd, *J* = 20.4, 4.2 Hz), 102.8, 67.4, 66.6, 54.1, 53.5, 42.4, 35.1, 34.6, 34.0, 24.8, 22.4, 18.2, 16.8, 12.2. mp 85-86 °C. FT-IR(neat) cm^{-1} 2947, 1594, 1479, 1345. HRMS (ESI) calcd. $C_{15}H_{10}F_4NO_6^-$ 376.0450 observed 376.0424.

Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(methoxycarbonyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4e)



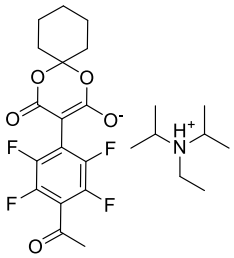
The general procedure **A** was followed using methyl-2,3,4,5,6-pentafluorobenzoate (124.3 µL, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid (92.0 mg, 0.5 mmol, 1.0 equiv), *i*Pr_2NEt (260 µL, 1.5 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4e** in 80% yield as colorless crystals (207.6 mg, 0.4 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.2 – -136.3 (m, 2F), -142.8 – -143.0 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.58 (hept, *J* = 6.5 Hz, 2H), 3.09 – 2.99 (m, 2H), 2.09 – 1.98 (m, 4H), 1.71 – 1.56 (m, 4H), 1.45 – 1.29 (m, 17H). ^{13}C (101 MHz, $CDCl_3$) δ 164.5, 161.1, 146.7 – 143.7 (m, overlapped), 146.1 – 143.0 (m, overlapped), 121.6 (t, *J* = 18.7 Hz), 108.0 (t, *J* = 15.4 Hz), 102.5, 66.7, 54.0, 52.7, 42.3, 34.6, 24.9, 22.5, 18.2, 16.9, 12.1. mp 119-121 °C. FT-IR(neat) cm^{-1} 2991, 2953, 1744, 1595, 1300. HRMS (ESI) calcd. $C_{17}H_{13}F_4O_6^-$ 389.0654 observed 389.0629.

Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 3-(2,3-difluoro-4-nitrophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4f)



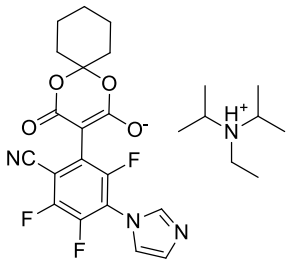
The general procedure **A** was followed using 1,2,3-trifluoro-4-nitrobenzene (63.2 µL, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid (92.0 mg, 0.5 mmol, 1.0 equiv), *i*Pr_2NEt (260 µL, 1.5 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4f** in 98% yield as orange crystals (230.0 mg, 0.49 mmol). The isolated product contained *ortho* and *para* substituted compounds in 4.1:1 ratio as determined by the ^{19}F NMR of the isolated material. ^{19}F NMR of the mixture (376 MHz, $CDCl_3$) δ -129.5 (major, d, *J* = 22.5 Hz, 1F), -130.3 (minor, d, *J* = 27.1 Hz, 1F), -130.6 (major, d, *J* = 8.4 Hz, 1F), -144.6 (minor, d, *J* = 15.1 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.63 (minor, m, 2H), 7.57 (major, ddd, *J* = 9.1, 4.8, 1.8 Hz, 1H), 7.05 – 6.92 (major, m, 1H), 3.66 – 3.48 (major, m, 2H), 3.02 (major, q, *J* = 7.2 Hz, 2H), 2.16 – 1.95 (major, m, 4H), 1.72 – 1.57 (major, m, 4H), 1.50 – 1.27 (major, m, 17H). ^{13}C of the mixture (101 MHz, $CDCl_3$) δ 164.64 , 164.55, 152.0 (dd, *J* = 407.5, 13.2 Hz), 152.0 – 147.2 (m, overlapped), 151.8 – 147.1 (m, overlapped), 151.7 – 147.2 (m, overlapped), 149.5 – 146.7 (m, overlapped), 149.4, 146.9, 146.2, 146.8, 136.6 (d, *J* = 11.3 Hz), 132.8 (d, *J* = 4.0 Hz), 125.9, 124.3 (d, *J* = 15.8 Hz), 119.9 (dd, *J* = 8.3, 3.7 Hz), 118.6, 112.8 (d, *J* = 19.4 Hz), 102.4, 101.8, 73.7, 69.7, 53.9, 42.2, 35.3, 34.7, 34.0, 24.9, 22.5, 22.4, 22.4, , 18.2, 16.9, 12.1. mp 130-133 °C. FT-IR(neat) cm^{-1} 2991, 1678, 1592, 1213. HRMS (ESI) calcd. $C_{15}H_{12}F_2NO_6^-$ 340.0638 observed 340.0619.

Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-acetyl-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4g)



The general procedure **A** was followed using 2′,3′,4′,5′,6′-pentafluoroacetophenone (142.3 µL, 1.0 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid (92.0 mg, 0.5 mmol, 1.0 equiv), *i*Pr_2NEt (260 µL, 1.5 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4g** in 95% yield as a yellow solid (239 mg, 0.48 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.1 – -136.4 (m, 2F), -144.8 – -145.0 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (hept, *J* = 6.6 Hz, 2H), 3.01 (q, *J* = 7.4 Hz, 2H), 2.07 – 2.01 (m, 4H), 2.00 (s, 3H), 1.66 (p, *J* = 6.4 Hz, 4H), 1.51 – 1.19 (m, 17H). ^{13}C (101 MHz, $CDCl_3$) δ 193.0, 164.5, 146.7 – 143.7 (m), 143.9 (dddd, *J* = 251.3, 16.3, 7.0, 4.0 Hz), 121.2 (t, *J* = 18.7 Hz), 115.4 (t, *J* = 16.1 Hz), 102.6, 66.8, 54.1, 42.4, 34.6, 32.4, 24.9, 22.5, 18.2, 16.8, 12.2. mp 58-60 °C. FT-IR(neat) cm^{-1} 2943, 1599, 1314. HRMS (ESI) calcd. $C_{17}H_{13}F_4O_5^-$ 373.0705 observed 373.0677.

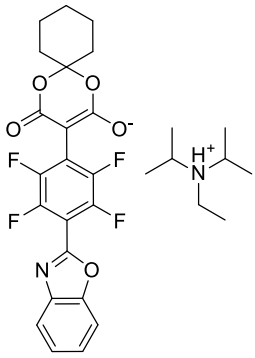
Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 3-(2-cyano-3,4,6-trifluoro-5-(1H-imidazol-1-yl)phenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4h)



The general procedure **A** was followed using 2,3,5,6-tetrafluoro-4-(1H-imidazol-1-yl)benzonitrile (132.5 mg, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid (92.0 mg, 0.5 mmol, 1.0 equiv), *i*Pr_2NEt (260 µL, 1.5 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4h** in 88% yield as a brown solid (236 mg, 0.44 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.2 (d, *J* = 13.2 Hz, 1F), -134.9 (dd, *J* = 21.2, 13.2 Hz, 1F), -146.5 (d, *J* = 21.2 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 1.5 Hz, 1H), 7.19 (s, 1H), 3.62 (hept, *J* = 6.7 Hz, 2H), 3.07 (q, *J* = 7.4 Hz, 2H), 2.15 – 1.90 (m, 4H), 1.75 – 1.11 (m, 21H). ^{13}C (101 MHz, $CDCl_3$) δ 164.5,

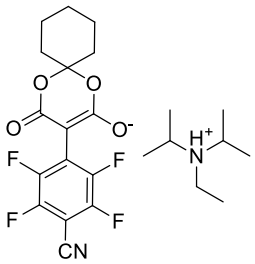
151.2, 148.7, 149.8 – 142.5 (m), 147.1 – 140.0 (m), 129.3, 127.6 (dd, *J* = 20.9, 3.8 Hz), 120.1, 119.7 (dd, *J* = 19.9, 11.4 Hz), 112.2 (t, *J* = 3.6 Hz), 105.0 (dd, *J* = 10.5, 5.5 Hz), 102.7, 70.4, 53.9, 42.2, 34.6 (d, *J* = 14.7 Hz), 24.7, 22.4, 18.3, 17.0, 12.1. mp 80-82 °C. FT-IR(neat) cm^{-1} 2938, 1681, 1589, 1482. HRMS (ESI) calcd. $C_{19}H_{13}F_3N_3O_4^-$ 404.0864 observed 404.0852.

Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-(2,7a-dihydrobenzo[d]oxazol-2-yl)-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4i)



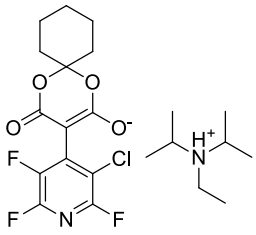
The general procedure **A** was followed using 2-(perfluorophenyl)benzo[d]oxazole (156.8 mg, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid (92.0 mg, 0.5 mmol, 1.0 equiv), *i*Pr_2NEt (260 µL, 1.5 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4i** in 82% yield as a yellow oil (237 mg, 0.41 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.9 – -136.0 (m, 2F), -141.6 – -141.7 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.61 (m, 2H), 7.46 – 7.35 (m, 2H), 3.61 (hept, *J* = 6.8, 6.3 Hz, 2H), 3.05 (q, *J* = 7.3 Hz, 2H), 2.11 – 2.04 (m, 4H), 1.67 (m, 4H), 1.47 – 1.33 (m, 17H). ^{13}C (101 MHz, $CDCl_3$) δ 164.4, 154.2, 150.1, 145.5 (dddd, *J* = 244.3, 11.3, 6.2, 3.3 Hz), 144.7 (ddt, *J* = 255.5, 16.7, 4.9 Hz), 141.0, 125.8, 124.7, 121.3 (t, *J* = 18.7 Hz), 120.2, 110.6, 103.6 (t, *J* = 13.7 Hz), 102.5, 66.9, 54.0, 42.3, 34.5, 24.8, 22.4, 18.1, 16.7, 12.1. FT-IR cm^{-1} 2942, 1686, 1597, 1488, 1304. HRMS (ESI) calcd. $C_{22}H_{16}F_4NO_5^-$ 450.0970 observed 450.0950.

Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-cyano-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4j)



This reaction was carried out in a borosilicate test tube. The general procedure **A** was followed using 2,3,4,5,6-pentafluorobenzonitrile (1.0 g, 5.42 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid (0.5 g, 2.71 mmol, 1.0 equiv), *i*Pr_2NEt (1.41 mL, 8.1 mmol, 3.0 equiv) and CH_3CN (27 mL). After the completion of the reaction the workup method **C** was used to isolate **4.4j** in 98% yield as a yellow solid (1.3 g, 2.66 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.3 – -133.6 (m, 2F), -136.4 – -136.7 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (hept, *J* = 10.0, 6.5, 3.2 Hz, 2H), 3.05 (qd, *J* = 7.4, 3.6 Hz, 2H), 2.06 – 2.00 (m, 4H), 1.66 (p, *J* = 6.7 Hz, 4H), 1.44 – 1.34 (m, 17H). ^{13}C (101 MHz, $CDCl_3$) δ 163.5, 146.2 (dd, *J* = 257.5, 16.9 Hz), 144.4 (d, *J* = 242.1 Hz), 125.2 (t, *J* = 18.2 Hz), 108.2, 102.2, 88.3, 66.7, 53.7, 42.0, 34.1, 24.3, 21.9, 17.6, 16.2, 11.7. mp 72-74 °C. FT-IR cm^{-1} 2948, 1594, 1481, 1291. HRMS (ESI) calcd. $C_{16}H_{10}F_4NO_4^-$ 356.0551 observed 356.0521.

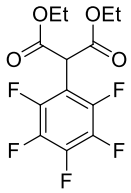
Synthesis of *N*-ethyl-*N*-isopropylpropan-2-aminium 3-(3-chloro-2,5,6-trifluoropyridin-4-yl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (4.4k)



The general procedure **A** was followed using 3-chloro-2,4,5,6-tetrafluoropyridine (22.6 µL, 0.2 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid (18.42 mg, 0.1 mmol, 1.0 equiv), *i*Pr_2NEt (52.0 µL, 0.3 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was used to isolate **4.4k** in 94% yield as a colorless oil (45.0 mg, 0.09 mmol). ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.6 – -77.0 (m, 1F), -93.4 – -93.6 (m, 1F), -138.1 (t, *J* = 24.6 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 – 3.50 (m, 2H), 3.04 (qd, *J* = 7.4, 4.0 Hz, 2H), 2.08 – 1.98 (m, 4H), 1.65 (p, *J* = 6.6 Hz, 4H), 1.50 – 1.32 (m, 17H). ^{13}C (101 MHz, $CDCl_3$)

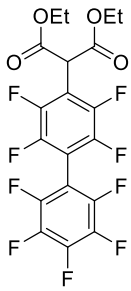
δ 164.0, 150.8 (ddd, *J* = 239.2, 13.7, 2.5 Hz), 146.9 (ddd, *J* = 243.2, 18.9, 15.2 Hz), 141.5 (ddd, *J* = 252.6, 24.4, 5.9 Hz), 115.4 (dd, *J* = 31.1, 5.9 Hz), 103.0, 71.2, 54.1, 42.4, 35.7, 33.8, 25.0, 22.6 (d, *J* = 22.6 Hz), 18.4, 17.1, 12.2. FT-IR cm^{-1} 2942,2 1599, 1434, 1216. HRMS (ESI) calcd. $C_{14}H_{10}ClF_3NO_4^-$ 348.0256 observed 348.0248.

Synthesis of diethyl 2-(perfluorophenyl)malonate (4.5a)



The general procedure **D** was followed using hexafluorobenzene (138 µL, 1.2 mmol, 1.2 equiv), diethyl malonate (153 µL, 1.0 mmol, 1.0 equiv), K_2CO_3 (414 mg, 3.0 mmol, 3.0 equiv) and DMF (0.6 mL). The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-4 cv, 0 %- 10% EtOAc for 4-9 cv, 10 % EtOAc for 9-11 cv, 10%-100% EtOAc for 11-16 cv, then held at 100% EtOAc 16-18 cv), on 4 g silica column to afford **4.5a** in 92% yield (300 mg, 0.92 mmol) as a colorless liquid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -139.9 – -140.1 (m, 2F), -153.4 (ddd, *J* = 21.0, 19.1, 1.7 Hz, 1F), -161.6 – -161.8 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.27 (qd, *J* = 7.1, 2.0 Hz, 4H), 1.29 (t, *J* = 7.1 Hz, 6H). ^{13}C (101 MHz, $CDCl_3$) δ 165.3, 145.4 (dtt, *J* = 249.8, 7.6, 3.7 Hz), 141.2 (dtd, *J* = 254.9, 13.4, 6.8 Hz), 139.1 – 136.0 (m), 108.4 (td, *J* = 17.0, 3.9 Hz), 62.5, 46.9, 13.6. FT-IR cm^{-1} 2987, 1751, 1508, 1307, 1224. HRMS (ESI) calcd. $C_{13}H_{11}F_5O_4$ 326.0577 observed 326.0562.

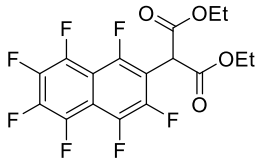
Synthesis of diethyl 2-(perfluoro-[1,1'-biphenyl]-4-yl)malonate (4.5b)



The general procedure **D** was followed using decafluorobiphenyl (80.2 mg, 0.24 mmol, 1.2 equiv), diethyl malonate (30.5 µL, 0.2 mmol, 1.0 equiv), K_2CO_3 (83 mg, 0.6 mmol, 3.0 equiv) and DMF (0.6 mL). The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-5 cv, 0 %-9% EtOAc for 5-10 cv, 9 % EtOAc for 10-15 cv, 9%-17% EtOAc for 15-18 cv, 17% EtOAc for 18-22 cv, 17%-100% EtOAc for 22-25 cv, then held at 100% EtOAc 25-27 cv), on 4 g

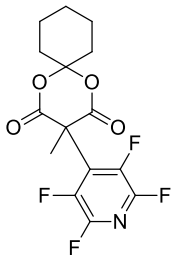
silica column to afford **4.5b** in 73% yield (69.0 mg, 0.15 mmol) as a white crystals. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.0 (dddd, *J* = 17.4, 11.8, 8.7, 5.8 Hz, 2F), -137.9 – -138.1 (m, 2F), -139.1 – -139.3 (m, 2F), -150.0 (tt, *J* = 20.8, 3.1 Hz, 1F), -160.3 – -160.5 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.32 (qq, *J* = 7.0, 3.6 Hz, 4H), 1.33 (t, *J* = 7.1 Hz, 6H). ^{13}C (101 MHz, $CDCl_3$) δ 165.3, 145.2 (dd, *J* = 251.9, 14.6 Hz), 144.5 (dd, *J* = 253.0, 18.3 Hz), 144.0 (ddt, *J* = 252.0, 14.9, 4.4 Hz), 141.2 (d, *J* = 13.5 Hz), 139.6 – 136.2 (m), 115.4 (t, *J* = 16.6 Hz), 106.6 (t, *J* = 17.8 Hz), 102.2 (t, *J* = 18.3 Hz), 62.8, 47.6, 13.9. mp 83-84 °C. FT-IR cm^{-1} 2989, 2926, 1739, 1477. HRMS (ESI) calcd. $C_{19}H_{11}F_9O_4$ 474.0514 observed 474.0523.

Synthesis of diethyl 2-(perfluoronaphthalen-2-yl)malonate (4.5c)



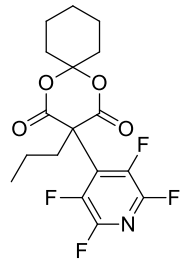
The general procedure **D** was followed using octafluoronaphthalene (65.3 mg, 0.24 mmol, 1.2 equiv), diethyl malonate (30.5 µL, 0.2 mmol, 1.0 equiv), K_2CO_3 (83 mg, 0.6 mmol, 3.0 equiv) and DMF (0.6 mL). The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-4 cv, 0%-10% EtOAc for 4-9 cv, 10 % EtOAc for 9-11 cv, 10%-100% EtOAc for 11-16 cv, then held at 100% EtOAc 16-18 cv), on 4 g silica column to afford **4.5c** in 75% yield (69.0 mg, 0.15 mmol) as a colorless liquid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.8 – -119.3 (m, 1F), -135.2 – -135.5 (m, 1F), -143.3 – -143.8 (m, 1F), -145.6 – -146.1 (m, 1F), -148.1 – -148.6 (m, 1F), -152.6 (q, *J* =20.8 Hz, 1F), -155.2 (d, *J* = 19.4 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.30 (q, *J* = 7.3, 6.5 Hz, 4H), 1.30 (t, *J* = 7.1 Hz, 6H). ^{13}C (101 MHz, Chloroform-*d*) δ 165.6, 150.7 (dd, *J* = 258.8, 4.1 Hz), 147.9 – 142.6 (m), 145.2 – 142.2 (m), 141.3 (t, *J* = 15.7 Hz), 140.1 (d, *J* = 4.8 Hz), 140.1 (dd, *J* = 34.4, 3.1 Hz), 138.1 (dt, *J* = 125.2, 16.7 Hz), 112.1 (t, *J* = 19.3 Hz), 111.6 (ddd, *J* = 15.5, 9.6, 2.8 Hz), 107.7 (dd, *J* = 18.1, 9.5 Hz), 62.7, 47.5, 13.9. FT-IR cm^{-1} 2987, 2942, 1745, 1655, 1497, 1441, 1409, 1181. HRMS (ESI) calcd. $C_{17}H_{11}F_7O_4$ 412.0546 observed 474.0541.

Synthesis of 3-methyl-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (4.7a)



The general procedure **E** was followed using pentafluoropyridine (54.9 µL, 0.5 mmol, 2.0 equiv), 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.25 mg, 0.25 mmol, 1.0 equiv), *i*Pr_2NEt (130.4 µL, 0.75 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was used to isolate **4.7a** in 96% yield as a white solid (83.6 mg, 0.24 mmol). The isolated product contained a mixture of the *para* and *ortho* isomers in 25:1 ratio as determined by the ^{19}F NMR of the isolated material. ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.1 – -89.3 (m, 2F), -138.9 – -139.2 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (t, *J* = 3.0 Hz, 3H), 2.05 (m, 4H), 1.87 – 1.74 (m, 4H), 1.60 – 1.50 (m, 2H). ^{13}C (101 MHz, $CDCl_3$) δ 165.6, 145.5 – 142.5 (m), 142.6 – 139.5 (m), 129.2 (tt, *J* = 11.7, 2.2 Hz), 109.0, 53.7, 37.5, 24.0 (t, *J* = 6.5 Hz), 23.8, 22.2 (d, *J* = 8.1 Hz). mp 100-101 °C. FT-IR cm^{-1} 2998, 2947, 1741, 1453, 1261. HRMS (ESI) calcd. $C_{15}H_{13}F_4NO_4$ 347.0781 observed 347.0772.

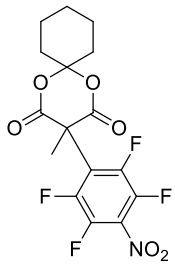
Synthesis of 3-(perfluoropyridin-4-yl)-3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (4.7b)



The general procedure **E** was followed using pentafluoropyridine (54.9 µL, 0.5 mmol, 2.0 equiv), 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (56.57 mg, 0.25 mmol, 1.0 equiv), *i*Pr_2NEt (130.4 µL, 0.75 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was used to isolate **4.7b** in >99% yield as a colorless liquid (94 mg, 0.25 mmol). The isolated product contained a mixture of the *para* and *ortho* isomers in 25:1 ratio as determined by the ^{19}F NMR of the isolated material. ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.0 – -89.5 (m, 2F), -137.5 (dd, *J* = 35.0, 14.9 Hz, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 – 2.49 (m, 2H), 2.02 (dt, *J*

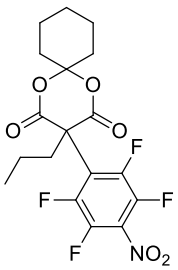
= 23.4, 6.2 Hz, 4H), 1.85 – 1.70 (m, 4H), 1.50 (dq, *J* = 24.0, 7.9, 7.1 Hz, 4H), 1.01 (t, *J* = 7.3 Hz, 3H). ^{13}C of the mixture (101 MHz, $CDCl_3$) δ 161.8, 160.7 , 141.8 – 138.8 (m), 138.7 – 135.5 (m), 124.6 (t, *J* = 11.5 Hz), 105.0, 101.7, 35.2 (t, *J* = 5.3 Hz), 34.4 (t, *J* = 2.4 Hz), 33.4, 33.0, 32.1, 20.1, 19.9, 18.6, 18.5, 18.1, 17.8, 16.0, 15.5, 10.0, 9.7. FT-IR cm^{-1} 2944, 2874, 1746, 1469, 1259. HRMS (ESI) calcd. $C_{17}H_{17}F_4NO_4$ 375.1094 observed 375.1063.

Synthesis of 3-methyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (4.7c)



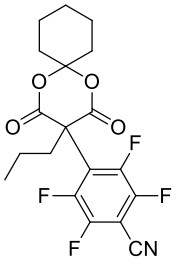
The general procedure **E** was followed using pentafluoronitrobenzene (33.3 µL, 0.275 mmol, 1.1 equiv), 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *i*Pr_2NEt (130.4 µL, 0.75 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was followed. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-2 cv, 0%-10% EtOAc for 2-6 cv, 10 % EtOAc for 6-11 cv, 10%-100% EtOAc for 11-16 cv, then held at 100% EtOAc 16-18 cv), on 4 g silica column to afford **4.7c** in 87% yield (85.0 mg, 0.21 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.3 (m, 2F), -145.3 – -145.5 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.2 (t, *J* = 3.1 Hz, 3H), 2.1 – 2.0 (m, 4H), 1.9 – 1.8 (m, 4H), 1.6 – 1.5 (m, 2H). ^{13}C (101 MHz, $CDCl_3$) δ 166.0, 146.1 (ddt, *J* = 254.0, 12.9, 5.6 Hz), 140.6 (ddd, *J* = 263.2, 17.5, 3.7 Hz), 120.5 (t, *J* = 13.1 Hz), 109.1, 51.2, 38.1, 37.6, 24.3 (t, *J* = 7.0 Hz), 24.0, 22.4 (d, *J* = 8.6 Hz). FT-IR cm^{-1} 2947, 1743, 1554, 1305. HRMS (ESI) calcd. $C_{16}H_{13}F_4NO_6$ 391.0679 observed 391.0665.

Synthesis of 3-propyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (4.7d)



The general procedure **E** was followed using pentafluoronitrobenzene (33.3 µL, 0.275 mmol, 1.1 equiv), 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *i*Pr_2NEt (130.4 µL, 0.75 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was followed. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-3 cv, 0%-10% EtOAc for 3-7 cv, 10 % EtOAc for 7-11 cv, 10%-30% EtOAc for 11-15 cv, 30%-100% EtOAc for 15-16, then held at 100% EtOAc 16-18 cv), on 4 g silica column to afford **5cb** in 81% yield (84.2 mg, 0.20 mmol) as yellow crystals. ^{19}F NMR (376 MHz, $CDCl_3$) δ -130.9 – -131.7 (m, 2F), -133.3 – -133.7 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 – 2.46 (m, 2H), 2.03 (dt, *J* = 24.4, 6.1 Hz, 4H), 1.80 (dp, *J* = 12.2, 6.2 Hz, 4H), 1.59 – 1.43 (m, 4H), 1.03 (t, *J* = 7.3 Hz, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 165.0, 146.1 (ddt, *J* = 253.7, 13.0, 5.8 Hz), 142.5 – 139.1 (m), 120.0 (t, *J* = 13.0 Hz), 109.1, 39.3 (t, *J* = 5.7 Hz), 38.4 (t, *J* = 2.3 Hz), 37.5, 24.0, 22.6, 22.2, 19.6, 13.7. mp 99-100 °C. FT-IR cm^{-1} 2953, 1737, 1253. HRMS (ESI) calcd. $C_{18}H_{17}F_4NO_6H$ 420.1070 observed 420.1051.

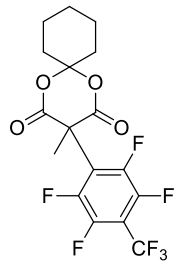
Synthesis of 4-(2,4-dioxo-3-propyl-1,5-dioxaspiro[5.5]undecan-3-yl)-2,3,5,6-tetrafluorobenzonitrile (4.7e)



The general procedure **E** was followed using pentafluorobenzonitrile (34.7 µL, 0.275 mmol, 1.1 equiv), 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *i*Pr_2NEt (130.4 µL, 0.75 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was followed. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-5 cv, 0%-10% EtOAc for 5-25 cv, 10 % EtOAc for 25-40 cv, 10%-40%

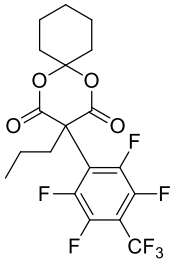
EtOAc for 40-60 cv, 40%-100% EtOAc for 60-65, then held at 100% EtOAc 65-67 cv), on 4 g silica column to afford **4.7e** in 85% yield (85.0 mg, 0.21 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.7 – -136.0 (m, 2F), -142.2 – -151.4 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 – 2.47 (m, 2H), 2.04 (dt, *J* = 24.4, 6.1 Hz, 4H), 1.80 (dp, *J* = 12.1, 6.3 Hz, 4H), 1.60 – 1.43 (m, 5H), 1.03 (t, *J* = 7.3 Hz, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 164.8, 147.5 (ddt, *J* = 262.8, 17.8, 3.8 Hz), 145.9 (ddt, *J* = 252.3, 12.6, 5.3 Hz), 122.1 (d, *J* = 12.9 Hz), 108.9, 106.7 (t, *J* = 3.7 Hz), 39.1 (t, *J* = 5.7 Hz), 38.3, 37.4, 23.9, 22.5, 22.1, 19.5, 13.6. FT-IR cm^{-1} 2944, 1744, 1491. HRMS (ESI) calcd. $C_{19}H_{17}F_4NO_4$ 399.1094 observed 399.1081.

Synthesis of 3-methyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (4.7f)



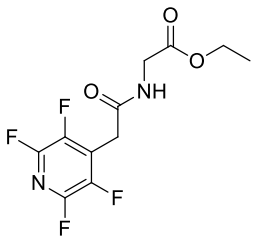
The general procedure **E** was followed using octafluorotoluene (70.8 µL, 0.50 mmol, 2.0 equiv), 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *i*Pr_2NEt (130.4 µL, 0.75 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was followed. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-6 cv, 0%-10% EtOAc for 6-23 cv, 10 % EtOAc for 23-35 cv, 10%-100% EtOAc for 35-45 cv, then held at 100% EtOAc 45-47 cv), on 4 g silica column to afford **4.7f** in 80% yield (83.0 mg, 0.20 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.6 (t, *J* = 21.4 Hz, 3F), -136.0 – -136.2 (m, 2F), -139.2 – -139.5 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (t, *J* = 3.0 Hz, 3H), 2.05 (dt, *J* = 16.9, 6.1 Hz, 4H), 1.80 (p, *J* = 6.1 Hz, 4H), 1.54 (p, *J* = 6.0 Hz, 2H). ^{13}C (101 MHz, $CDCl_3$) δ 166.1, 146.0 (ddt, *J* = 251.2, 14.8, 5.2 Hz), 144.4 (dd, *J* = 261.6, 17.5 Hz), 121.8, 120.4 (t, *J* = 13.0 Hz), 119.0, 108.8, 37.9, 37.6, 24.2 (t, *J* = 6.9 Hz), 23.9, 22.2 (d, *J* = 8.2 Hz). mp 100-102 °C. FT-IR cm^{-1}2944, 2856, 1736, 1142. HRMS (ESI) calcd.$C_{17}H_{13}F_7O_4H$ 415.0780 observed 414.0792.

Synthesis of 3-propyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (4.7g)



The general procedure **E** was followed using octafluorotoluene (70.8 µL, 0.50 mmol, 2.0 equiv), 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *i*Pr_2NEt (130.4 µL, 0.75 mmol, 3.0 equiv) and CH_3CN (0.5 mL). After the completion of the reaction the workup method **B** was followed. The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-2 cv, 0%-10% EtOAc for 2-6 cv, 10 % EtOAc for 6-8 cv, 10%-15% EtOAc for 8-10 cv, 15%-100% EtOAc for 10-12 cv, then held at 100% EtOAc 12-14 cv), on 4 g silica column to afford **4.7g** in 79% yield (88.3 mg, 0.19 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.7 (t, *J* = 21.3 Hz, 3F), -134.4 – -134.9 (m, 2F), -139.0 – -139.6 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 – 2.41 (m, 2H), 1.97 (dq, *J* = 12.2, 6.0 Hz, 4H), 1.73 (dp, *J* = 12.3, 6.5 Hz, 4H), 1.53 – 1.36 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 165.3, 147.7 – 144.6 (m), 146.4 – 143.0 (m), 120.0 (t, *J* = 12.9 Hz), 111.1 – 110.2 (m), 108.9, 39.4 (t, *J* = 5.6 Hz), 38.4 (t, *J* = 2.5 Hz), 37.6, 24.1, 22.6, 22.2, 19.6, 13.8. FT-IR cm^{-1} 2946, 2875, 1747, 1492, 13334. HRMS (ESI) calcd. $C_{19}H_{17}F_7O_4H$ 443.1093 observed 443.1095.

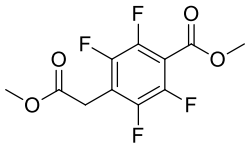
Synthesis of ethyl 2-(2-(perfluoropyridin-4-yl)acetamido)acetate (4.8a)



The general procedure **E** was followed using **2a** (46.2 mg, 0.1 mmol, 1.0 equiv) and ethyl 2-aminoacetate hydrochloride (41.9 mg, 0.3 mmol, 3.0 equiv) and dioxane (1.0 mL) to obtain **4.8a** in 94% yield (55.0 mg, 0.09 mmol) as an off-white solid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.0 – -91.3 (m, 2F), -143.4 – -143.6 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.2 Hz, 2H), 4.03 (d, *J* = 5.1 Hz, 2H), 3.81 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 169.7, 166.1, 144.8 – 141.7 (m), 142.4 – 141.8 (m), 128.0 (tt, *J* = 16.7, 2.9 Hz), 61.9, 41.8, 30.4, 14.1. mp 90-

92 °C. FT-IR cm^{-1} 3316, 2997, 1741, 1459, 1225. HRMS (ESI) calcd. $C_{11}H_{10}F_4N_2O_3$ 294.0628 observed 294.0642.

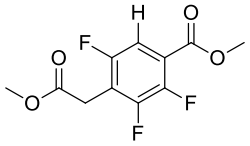
Synthesis of methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate (4.8c)



For the monitoring purposes, this reaction was carried out in an NMR tube and monitored *via* ^{19}F NMR. An NMR tube charged with **2d** (100 mg, 0.2 mmol, 1.0 equiv) and HCl (36% w/v, 20.6 µL, 0.24 mmol, 1.2 equiv) and methanol (0.5 mL) were added and sealed glass capillary containing C_6D_6 was placed in NMR tube for locking purposes. Then the NMR tube was placed in a sand bath and maintained at 80 °C. The reaction was periodically monitored by ^{19}F NMR. After the completion of the reaction, methanol was removed *in vacuo* and the resulting residue was dissolved in DCM (2 mL) and washed with deionized water (3 × 5 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to obtain the title compound **4.8c** in 95% yield (53.0 mg, 0.19 mmol) as a colorless liquid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -139.7 – -139.9 (m, 2F), -141.4 – -141.5 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 3.80 (t, *J* = 1.6 Hz, 2H), 3.75 (s, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 168.2, 160.0, 145.1 (ddt, *J* = 248.6, 14.3, 5.1 Hz), 144.4 (ddt, *J* = 256.5, 15.4, 4.6 Hz), 116.5 (t, *J* = 18.2 Hz), 111.8 (t, *J* = 15.9 Hz), 53.2, 52.7, 28.2. FT-IR cm^{-1} 2960, 1742, 1485, 1310. HRMS (ESI) calcd.$C_{11}H_8F_4O_4$ 280.0359 observed 280.0382.

Synthesis of methyl 2,3,5-trifluoro-4-(2-methoxy-2-oxoethyl)benzoate (4.8d)

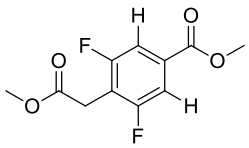
The general procedure **F** was followed using methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-



oxoethyl)benzoate (**4.8c**) (28.0 mg, 0.1 mmol, 1.0 equiv), *i*Pr_2NEt (19.2 µL, 0.11 mmol, 1.1 equiv). After the completion of the reaction the crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-1 cv, 0%-11% EtOAc for 1-3 cv, 11 % EtOAc for 3-4 cv, 11%-22% EtOAc for 4-5 cv, 22%-100% EtOAc for 5-8 cv, then held at 100% EtOAc 8-10 cv), on 4 g silica column to afford **4.8d** in 94%

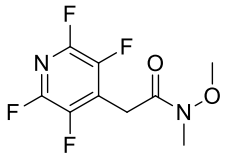
yield (25.0 mg, 0.09 mmol) as a colorless oil. The isolated product also contained 2% starting material and 4% di-hydrodefluorinated product. ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.7 – -118.8 (m, 1F), -135.0 (d, *J* = 20.3 Hz, 1F), -139.0 (ddd, *J* = 20.7, 16.1, 5.1 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 1H), 3.88 (s, 3H), 3.71 (s, 2H), 3.67 (s, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 168.7, 163.0 (q, *J* = 3.4 Hz), 155.6 (ddd, *J* = 246.5, 6.5, 3.5 Hz), 149.9 (ddd, *J* = 251.4, 15.0, 8.1 Hz), 147.0 (ddd, *J* = 259.8, 14.5, 3.8 Hz), 119.3 (t, *J* = 8.9 Hz), 117.2 (dd, *J* = 22.2, 16.8 Hz), 112.3 (dd, *J* = 26.1, 3.8 Hz), 52.9, 52.6, 28.4. FT-IR cm^{-1} 2958, 1742, 1468, 1265. HRMS (ESI) calcd. $C_{11}H_9F_3O_4$ 262.0453 observed 262.0469.

Synthesis of methyl 3,5-difluoro-4-(2-methoxy-2-oxoethyl)benzoate (4.8e)



The general procedure **F** was followed using methyl-2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate (**4.8c**) (26.5 mg, 0.09 mmol, 1.0 equiv), *i*Pr_2NEt (99.0 µL, 0.57 mmol, 6.0 equiv). After the completion of the reaction the crude material was purified by passing through a short silica plug to afford **4.8e** in 92% yield (23.2 mg, 0.08 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.9 (d, *J* = 7.3 Hz, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 2H), 3.92 (s, 3H), 3.75 (s, 2H), 3.72 (s, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 164.8 (t, *J* = 3.3 Hz), 161.1 (dd, *J* = 249.6, 7.9 Hz), 131.6 (t, *J* = 9.5 Hz), 115.5 (t, *J* = 20.4 Hz), 112.4 (d, *J* = 27.1 Hz), 112.4 (d, *J* = 12.5 Hz), 52.6, 52.5, 28.0. FT-IR cm^{-1} 2957, 1730, 1586, 1430. HRMS (ESI) calcd. $C_{11}H_{10}F_2O_4$ 244.0547 observed 244.0529.

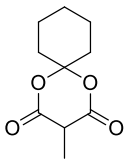
Synthesis of *N*-methoxy-*N*-methyl-2-(perfluoropyridin-4-yl)acetamide (4.8b)



The general procedure **E** was followed using **4.4a** (23.1 mg, 0.05 mmol, 1.0 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (11.8 mg, 0.12 mmol, 2.4 equiv) and dioxane (0.5 mL) to obtain **4.8b** in 90% yield (11.3 mg, 0.04 mmol) a yellow liquid. ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.0 – -91.3 (m, 2F), -143.6 – -

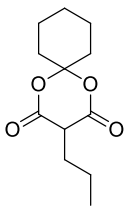
143.9 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 2H), 3.81 (s, 3H), 3.25 (s, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 167.01, 144.67 – 141.67 (m), 142.49 – 139.32 (m), 128.32 (tt, *J* = 17.5, 3.6 Hz), 61.48, 32.46, 27.60. FT-IR cm^{-1} 2937, 1710, 1471, 1047. HRMS (ESI) calcd. $C_9H_8F_4N_2O_2$ 252.0522 observed 252.0529.

Synthesis of 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione



The general procedure **G** was followed using formic acid (186 µL, 4.93 mmol), cyclohexyl-Meldrum's acid (1.0 g, 5.43 mmol), DMAP (60 mg, 0.49 mmol), *i*Pr_2NEt (1.8 mL, 10.6 mmol), DCC (1.4 g, 5.43 mmol), acetic acid (2.8 mL, 49.3 mmol), $NaBH_4$ (466 mg, 12.3 mmol) and MeCN (25 mL). The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-5 cv, 0 %-12% EtOAc for 5-15 cv, 12 % EtOAc for 15-25 cv, 12%-50% EtOAc for 25-30 cv, 50%-100% EtOAc for 30-37 cv, then held at 100% EtOAc 37-39 cv), on 40 g silica column to afford the title compound in 71% yield (971 mg, 3.5 mmol) as a white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (q, *J* = 7.1 Hz, 1H), 2.07 – 1.91 (m, 4H), 1.84 – 1.64 (m, 4H), 1.63 – 1.46 (m, 5H). ^{13}C (101 MHz, $CDCl_3$) δ 166.1, 105.6, 41.4, 36.9, 35.1, 24.0, 22.5, 21.8, 10.6, which matched with the literature (ref-Ziegler, E.; Junek, H.; Kroboth, H. *Monatsh. Chem*. **1976**, 107, 317).

Synthesis of 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione

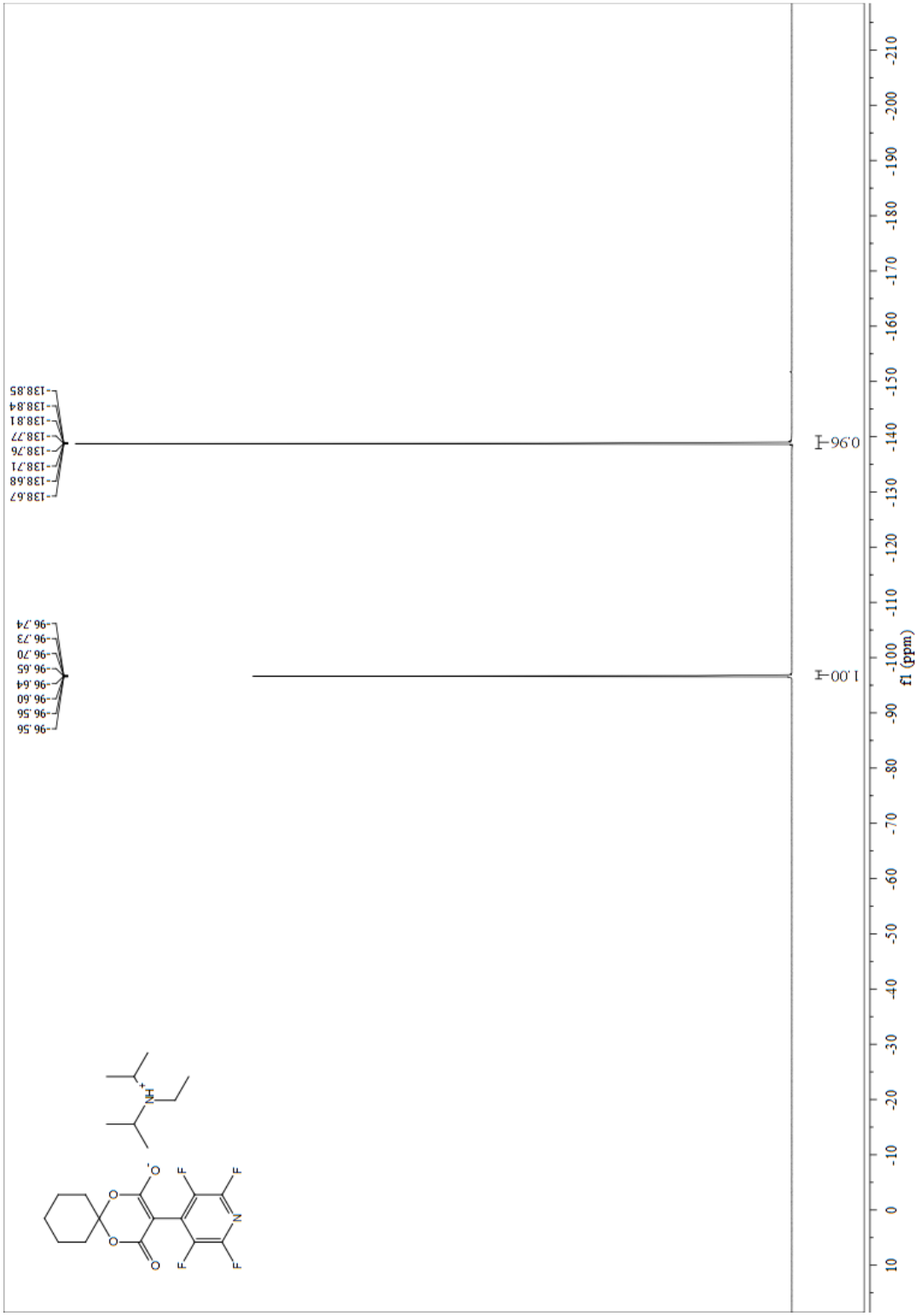


The general procedure **G** was followed using propionic acid (369 µL, 4.93 mmol), cyclohexyl-Meldrum's acid (1.0 g, 5.43 mmol), DMAP (60 mg, 0.49 mmol), *i*Pr_2NEt (1.8 mL, 10.6 mmol), DCC (1.4 g, 5.43 mmol), acetic acid (2.8 mL, 49.3 mmol) and $NaBH_4$ (466 mg, 12.3 mmol). The crude material was purified by flash chromatography using hexane : ethyl acetate (0 % EtOAc for 0-3 cv, 0 %-9% EtOAc for 3-11 cv, 9 % EtOAc for 11-30 cv, 9%-35% EtOAc for 30-37 cv, 35% EtOAc for 37-45 cv, 35%-70% EtOAc for 45-50 cv, 70% EtOAc for 50-55 cv, 70%-100% EtOAc for 55-65 cv, then held at

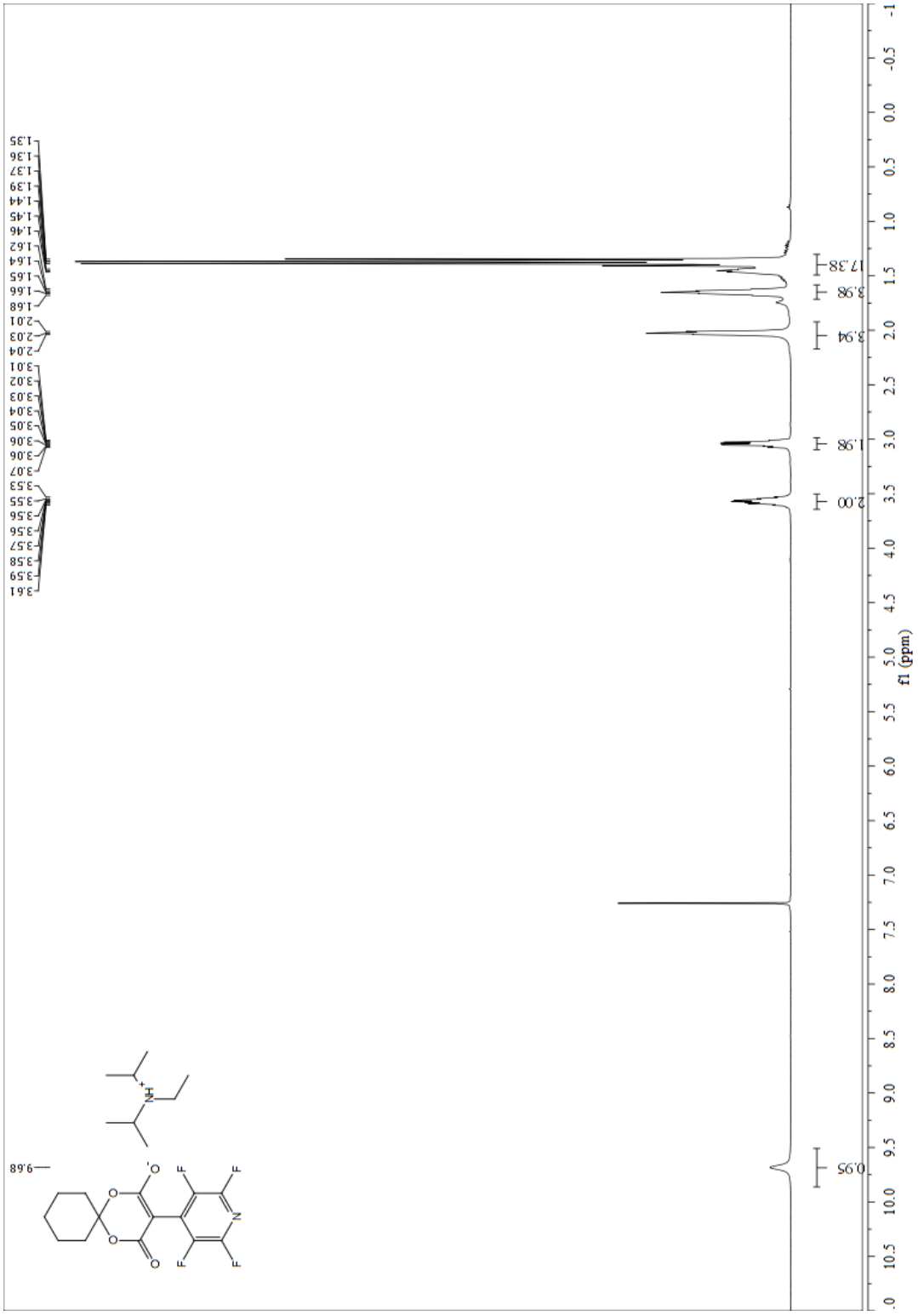
100% EtOAc 65-67 cv), on 40 g silica column to afford the title compound in 92% yield (1.0 g, 4.5 mmol) as a white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (t, *J* = 5.1 Hz, 1H), 2.11 – 2.03 (m, 2H), 2.03 – 1.89 (m, 4H), 1.83 – 1.62 (m, 4H), 1.55 – 1.39 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C (101 MHz, $CDCl_3$) δ 165.6, 105.5, 46.1, 36.8, 35.7, 28.6, 24.0, 22.5, 21.7, 19.7, 13.8, which matched with the literature (ref- Ziegler, E.; Junek, H.; Kroboth, H. *Monatsh. Chem.* **1976**, 107, 317).

NMR, GC and MS spectra for Chapter IV

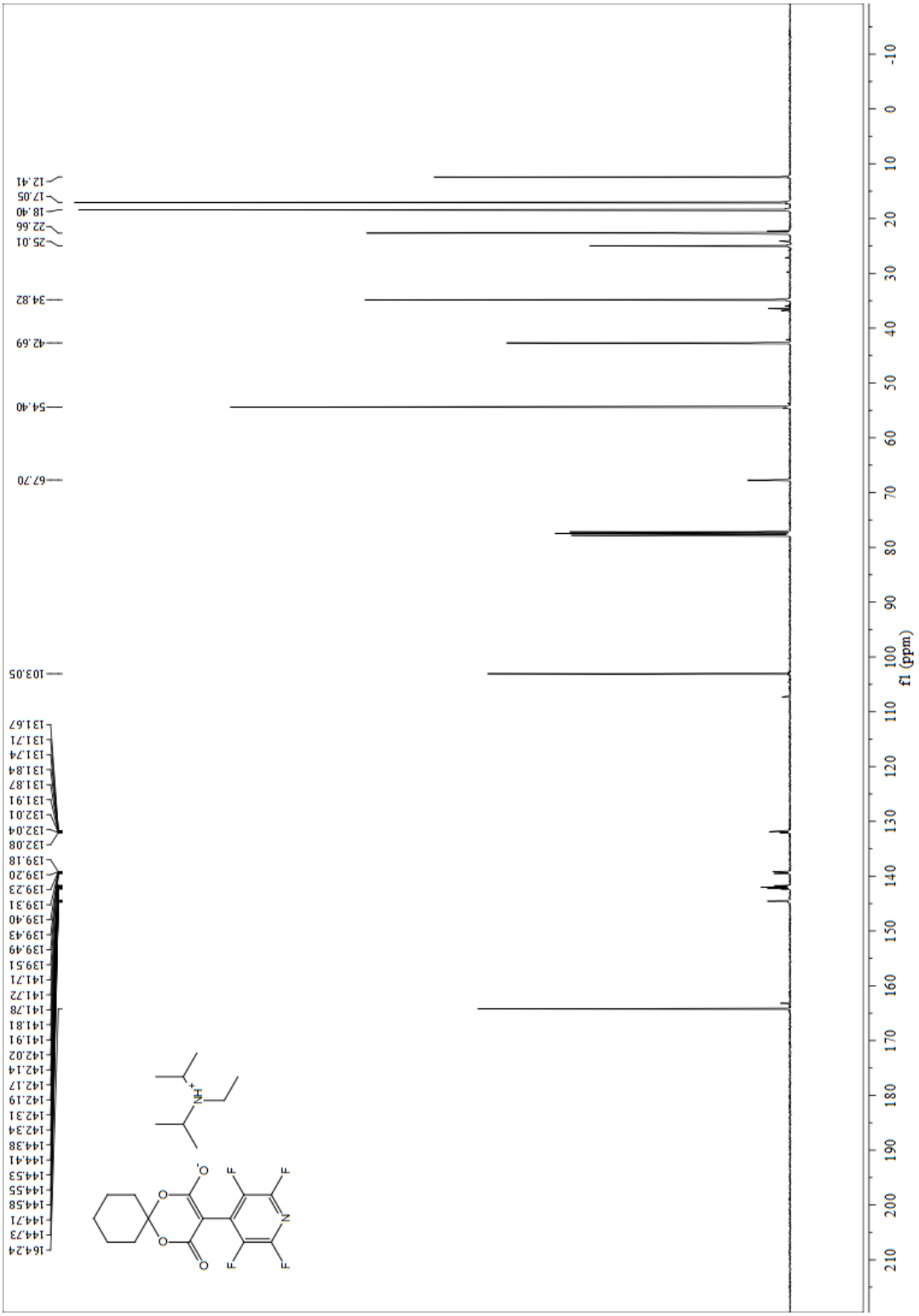
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4a (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



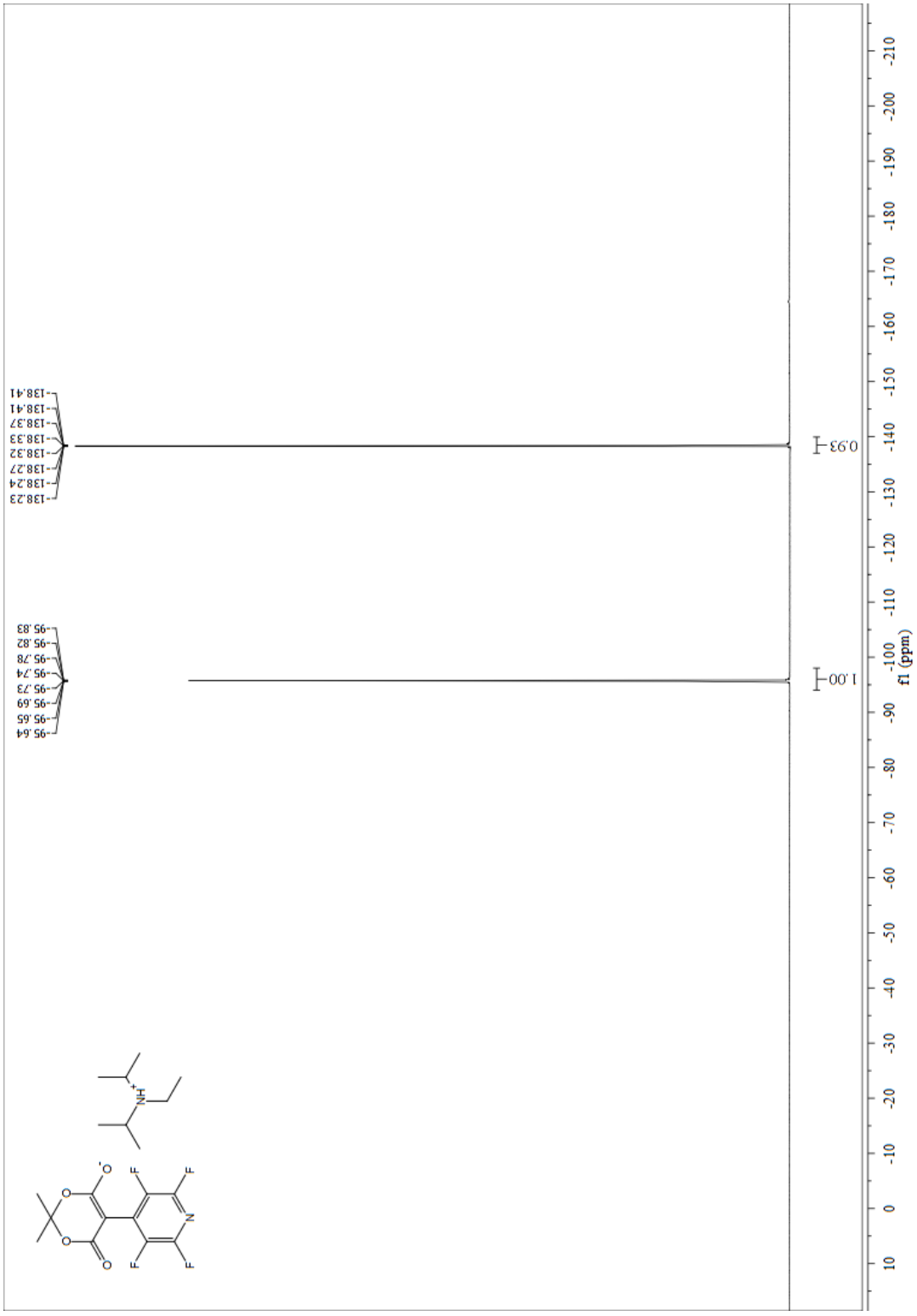
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4a (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



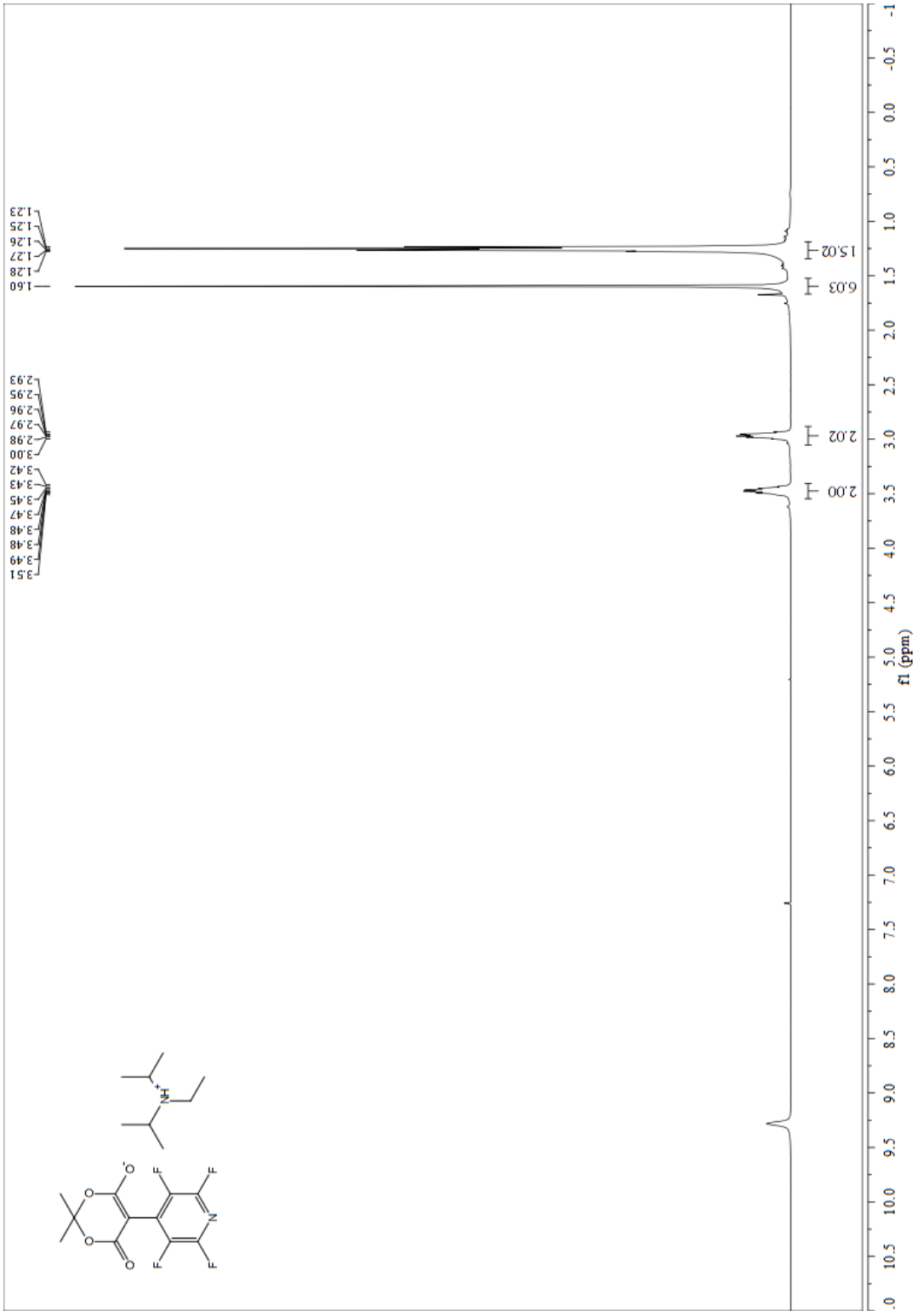
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4a (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



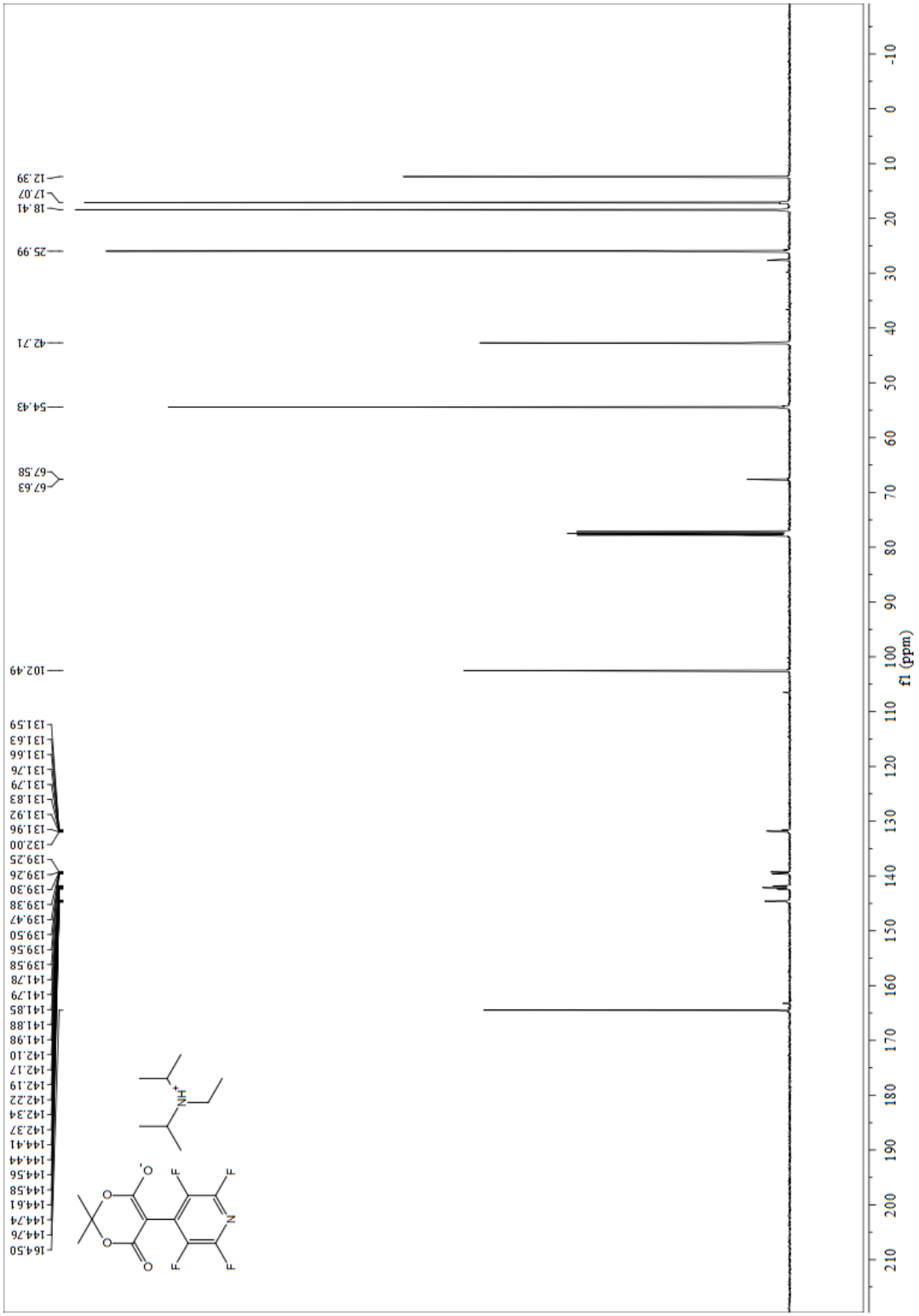
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4b (*N*-ethyl-*N*-isopropylpropan-2-aminium 2,2-dimethyl-4-oxo-5-(perfluoropyridin-4-yl)-4H-1,3-dioxin-6-olate)



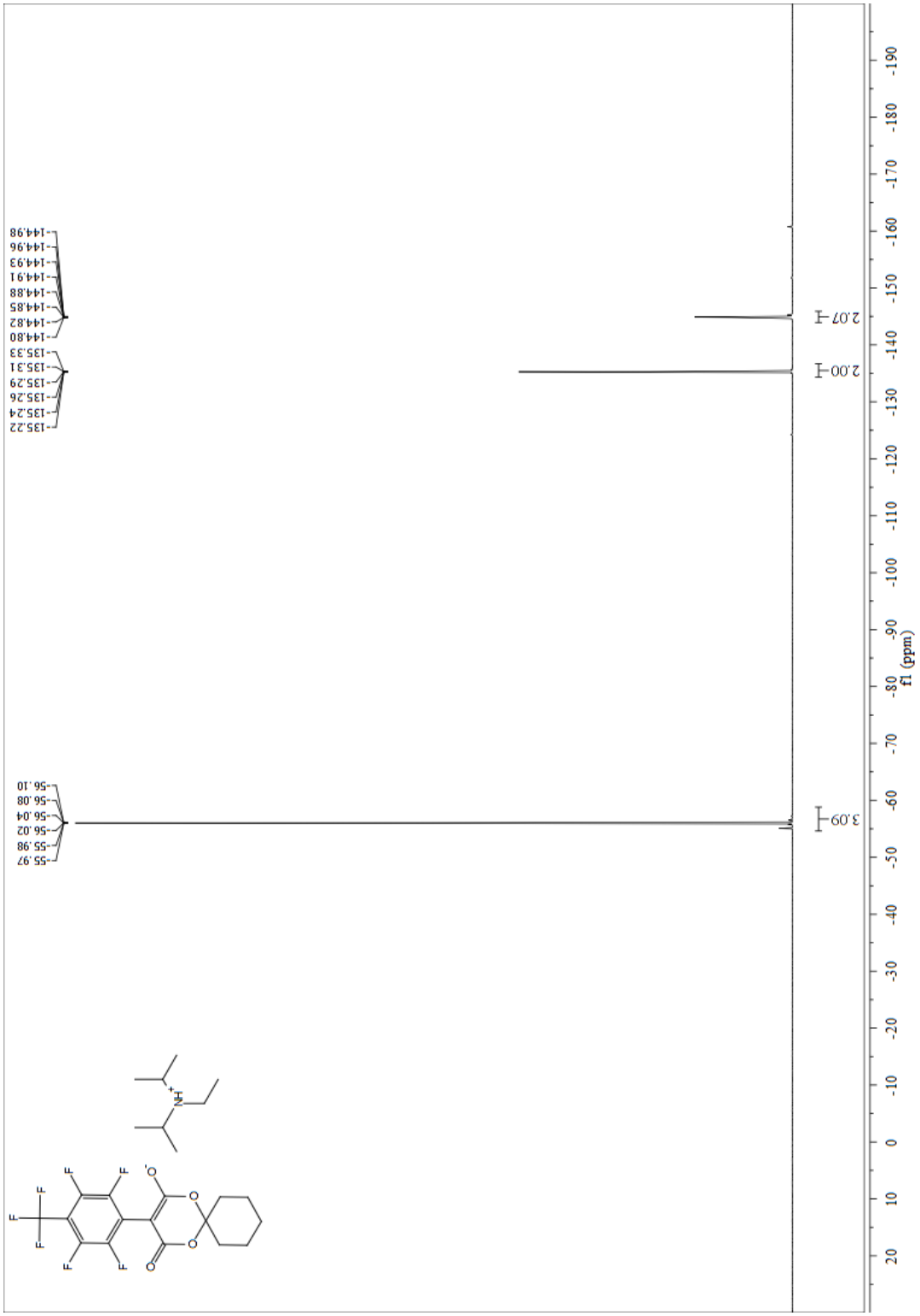
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4b (*N*-ethyl-*N*-isopropylpropan-2-aminium 2,2-dimethyl-4-oxo-5-(perfluoropyridin-4-yl)-4H-1,3-dioxin-6-olate)



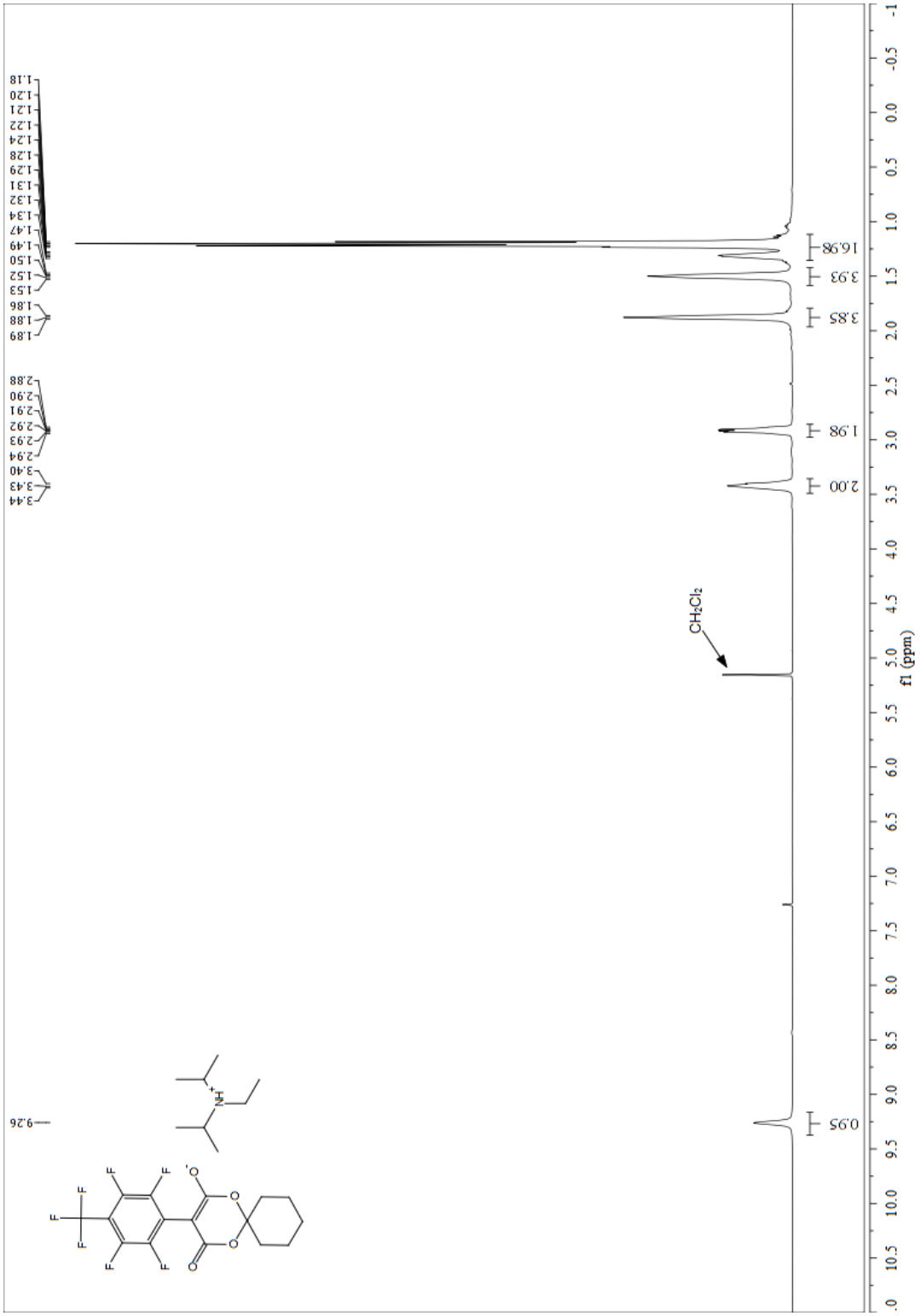
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4b (*N*-ethyl-*N*-isopropylpropan-2-aminium 2,2-dimethyl-4-oxo-5-(perfluoropyridin-4-yl)-4H-1,3-dioxin-6-olate)



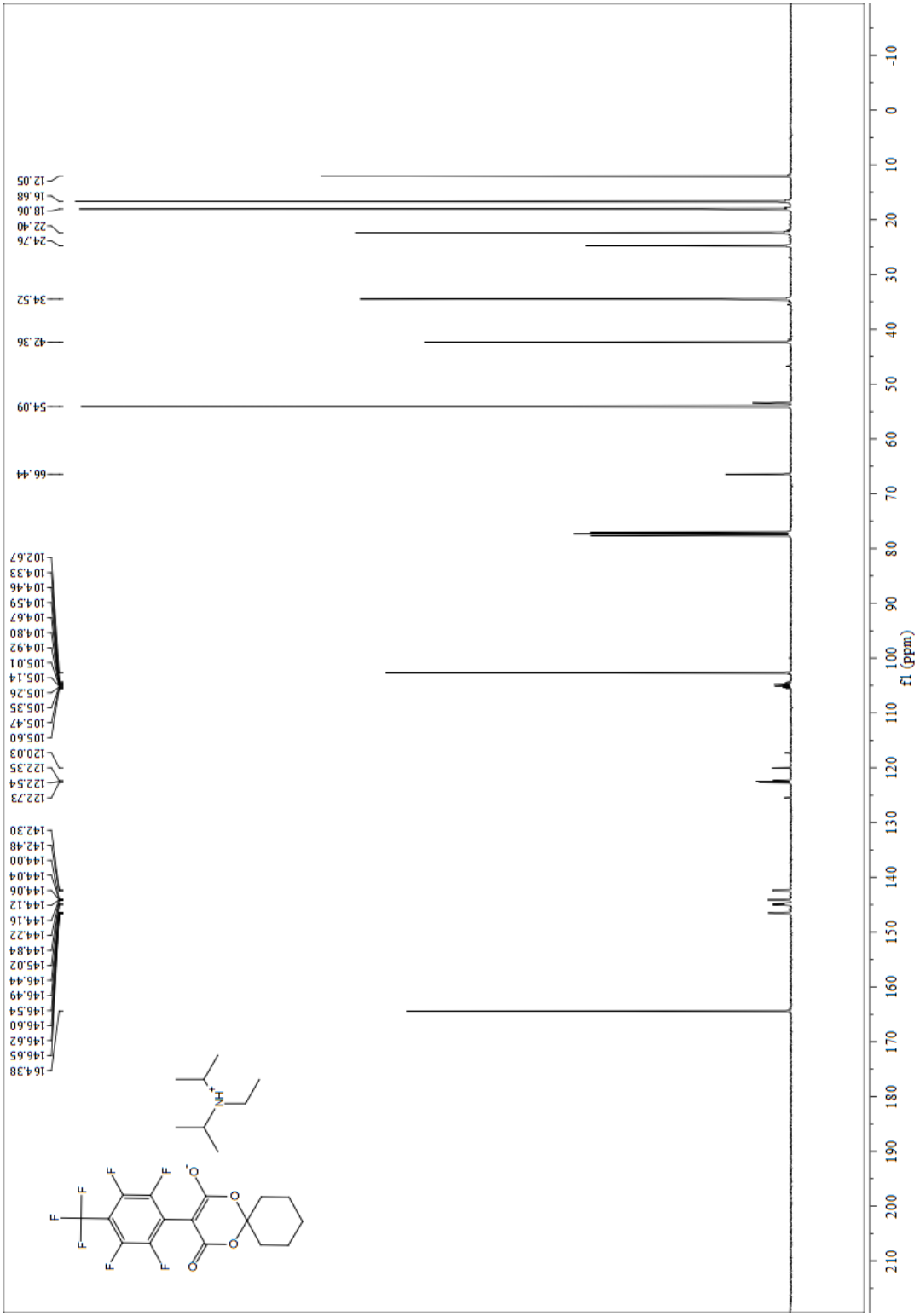
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4c (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



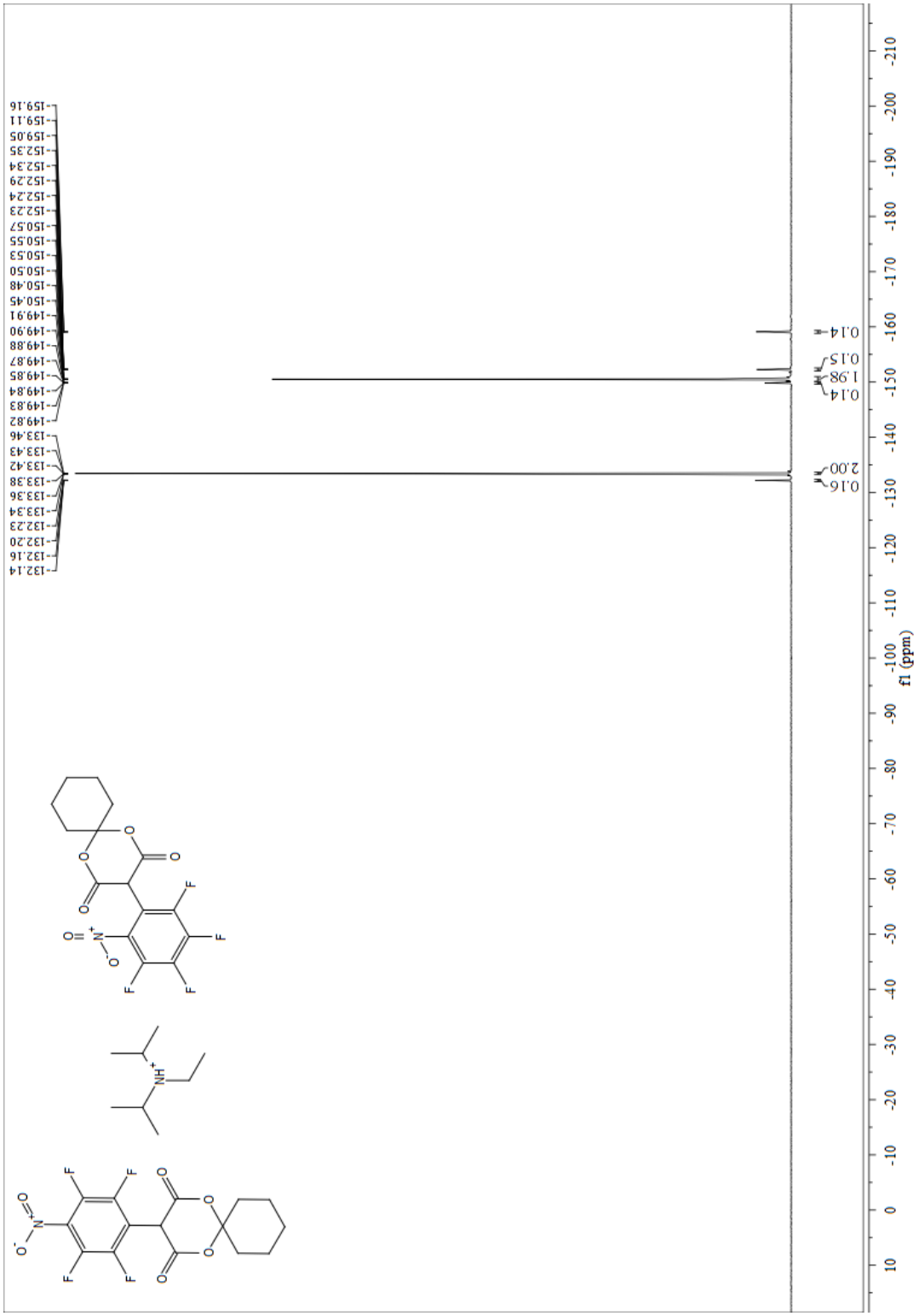
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4c (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



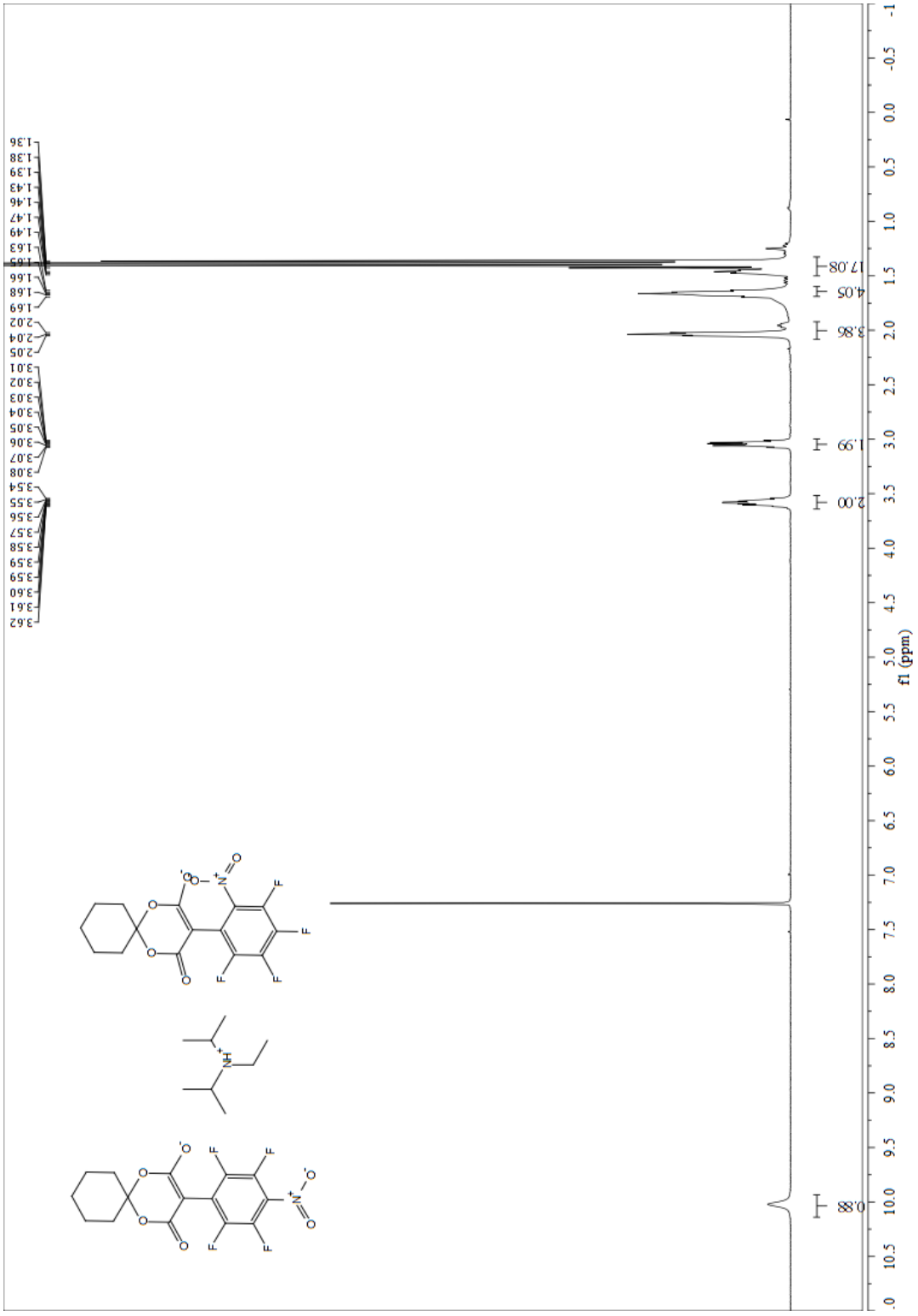
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4c (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



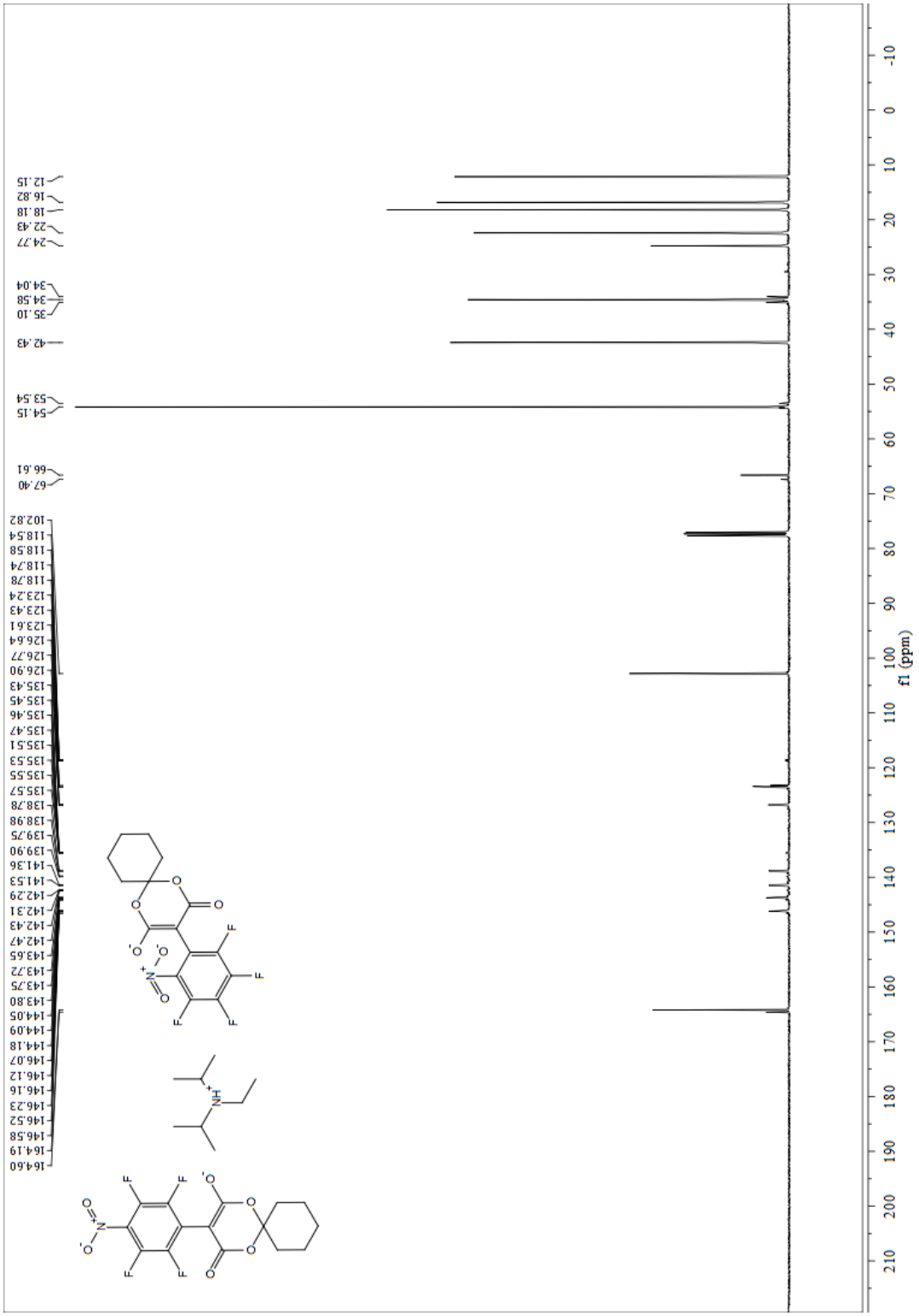
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4d (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



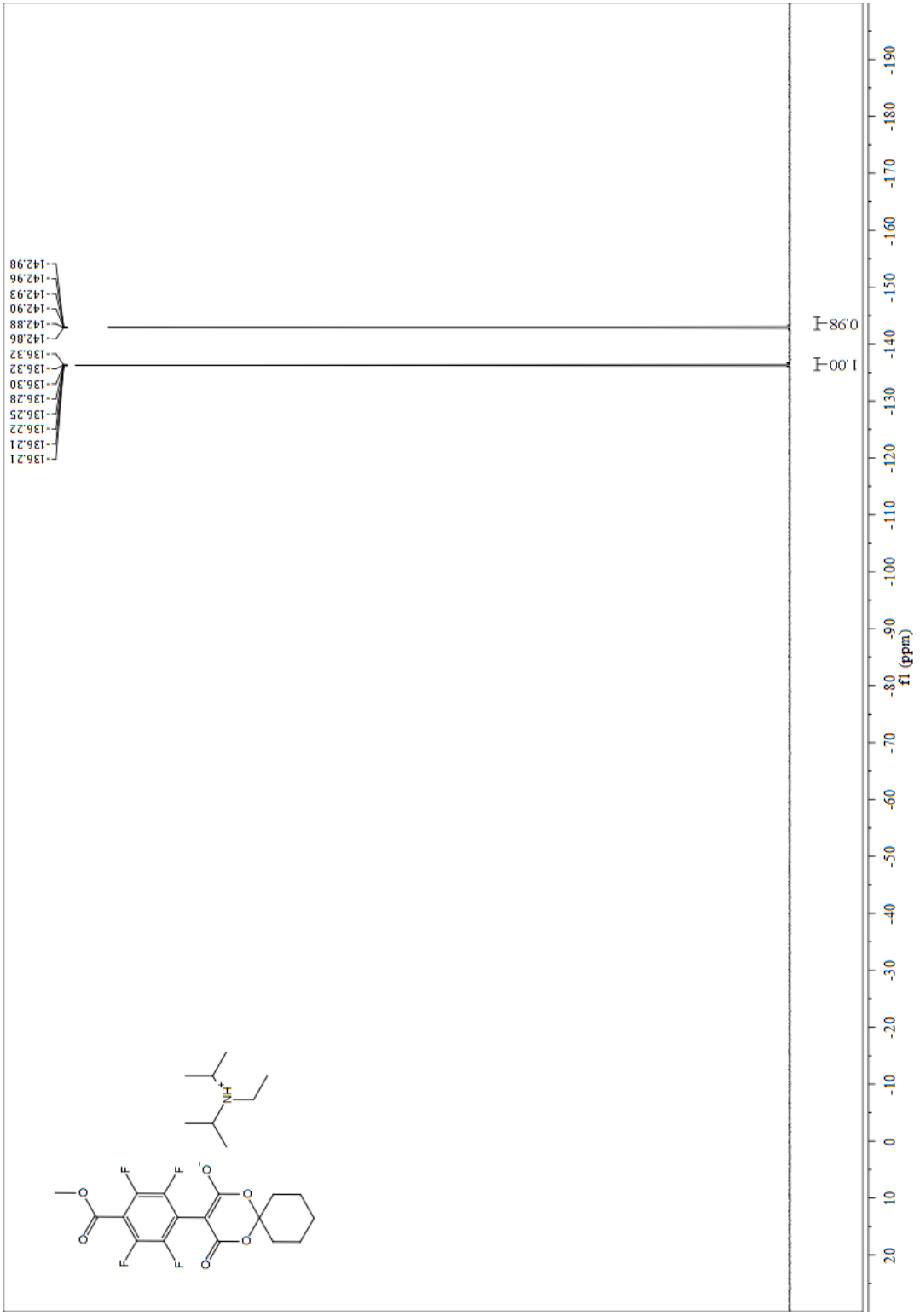
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4d (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



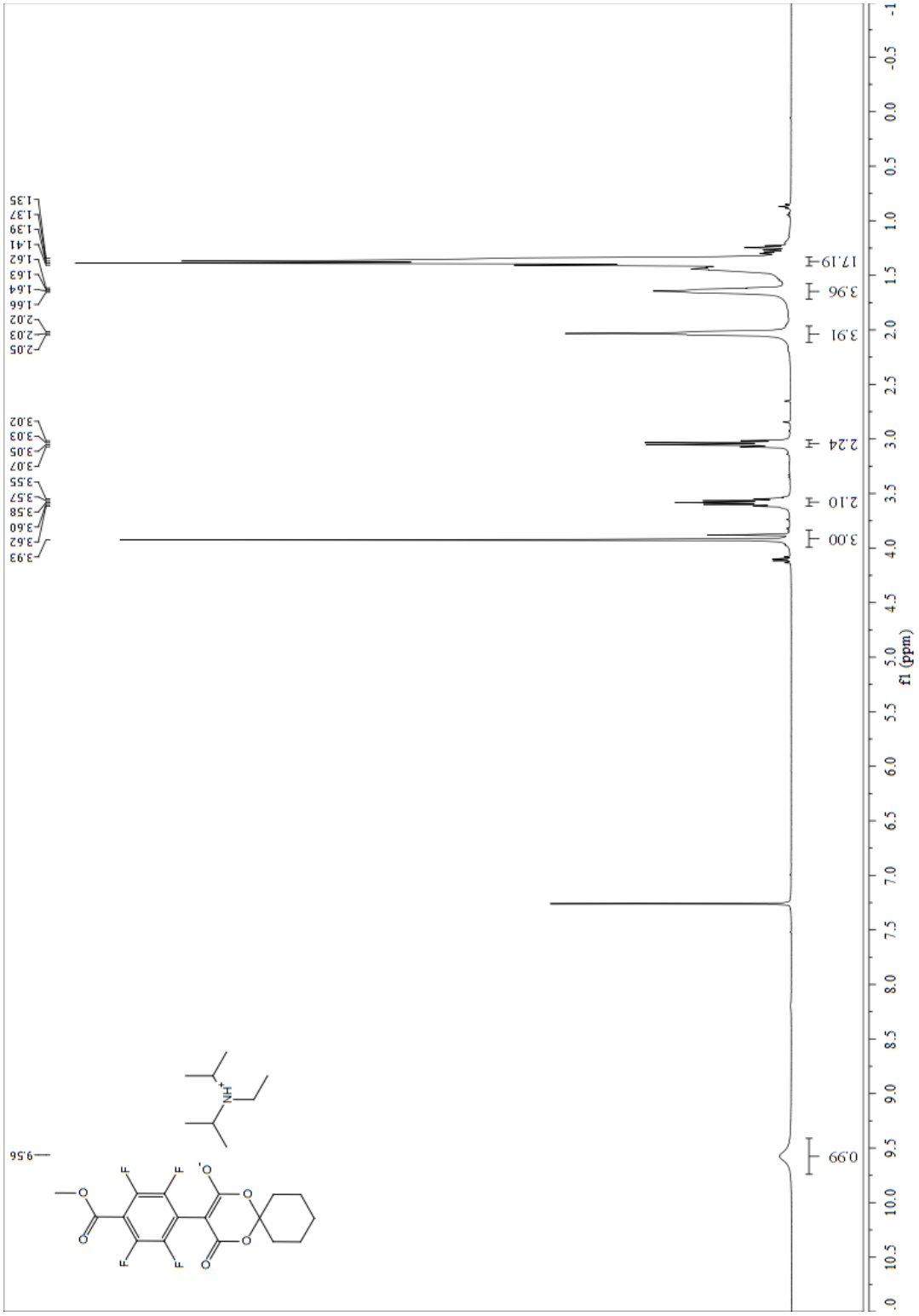
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4d (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



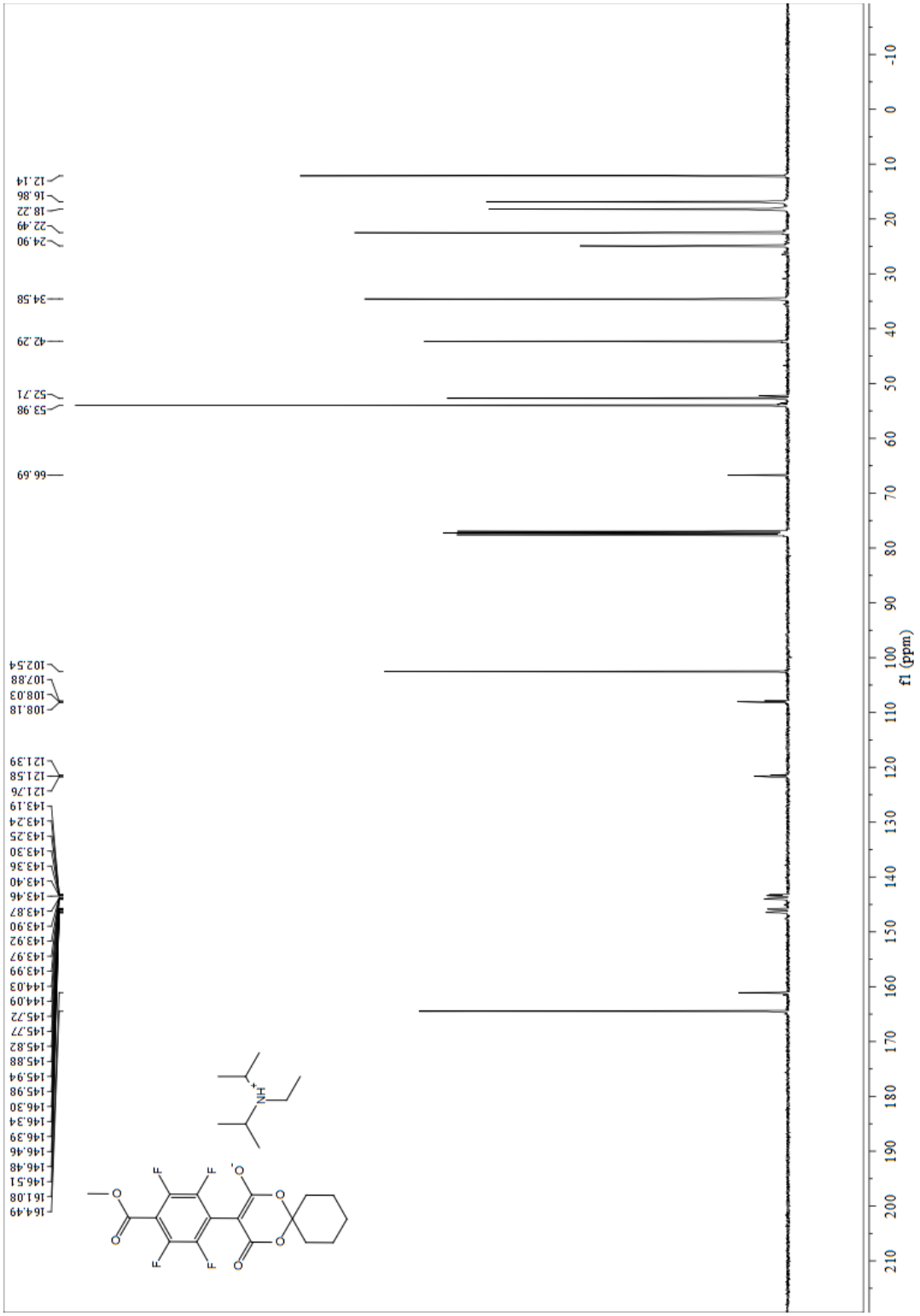
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4e (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(methoxycarbonyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



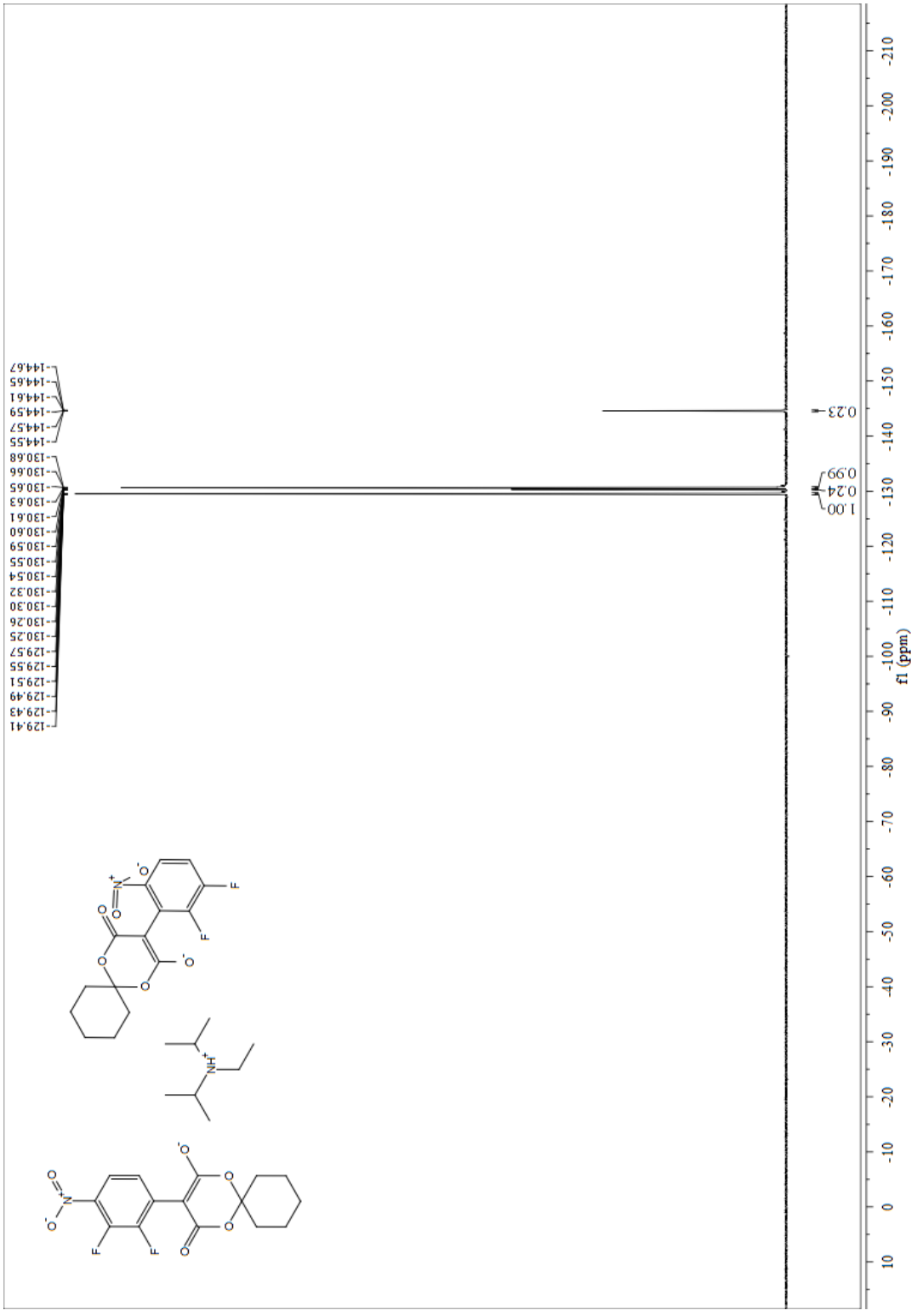
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4e (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(methoxycarbonyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



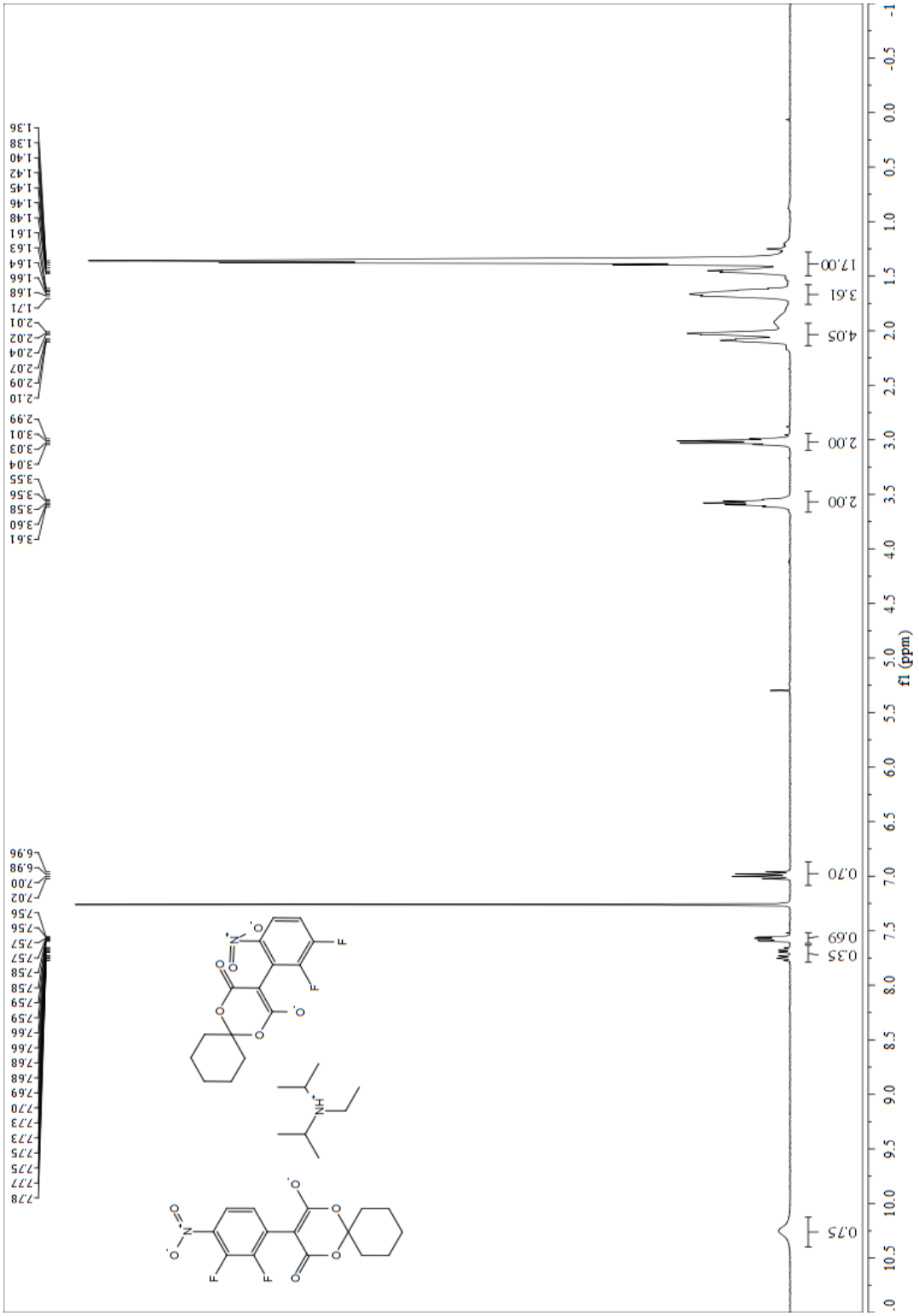
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4e (*N*-ethyl-*N*-isopropylpropan-2-aminium 4-oxo-3-(2,3,5,6-tetrafluoro-4-(methoxycarbonyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



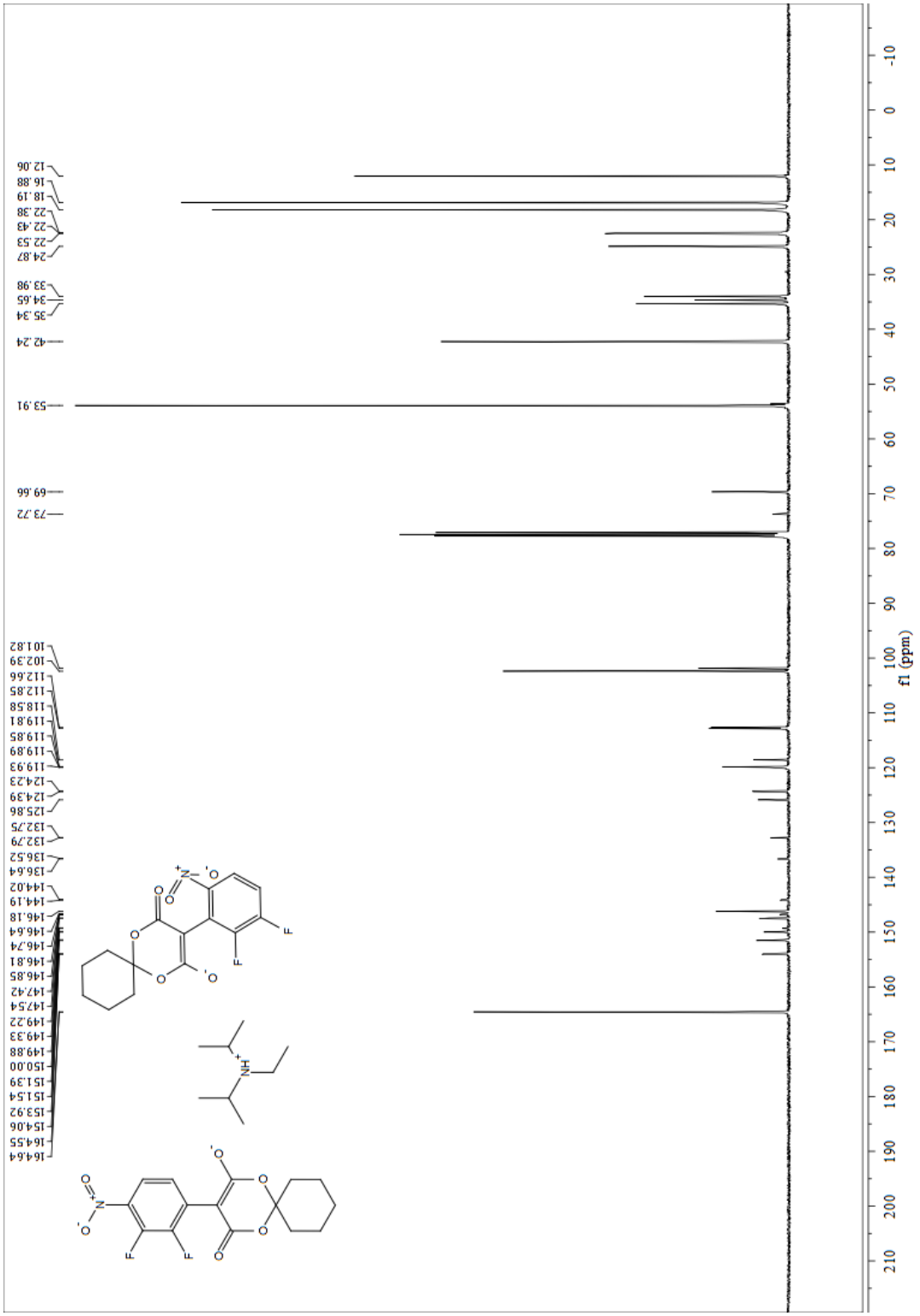
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4f (*N*-ethyl-*N*-isopropylpropan-2-aminium3-(2,3-difluoro-4-nitrophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



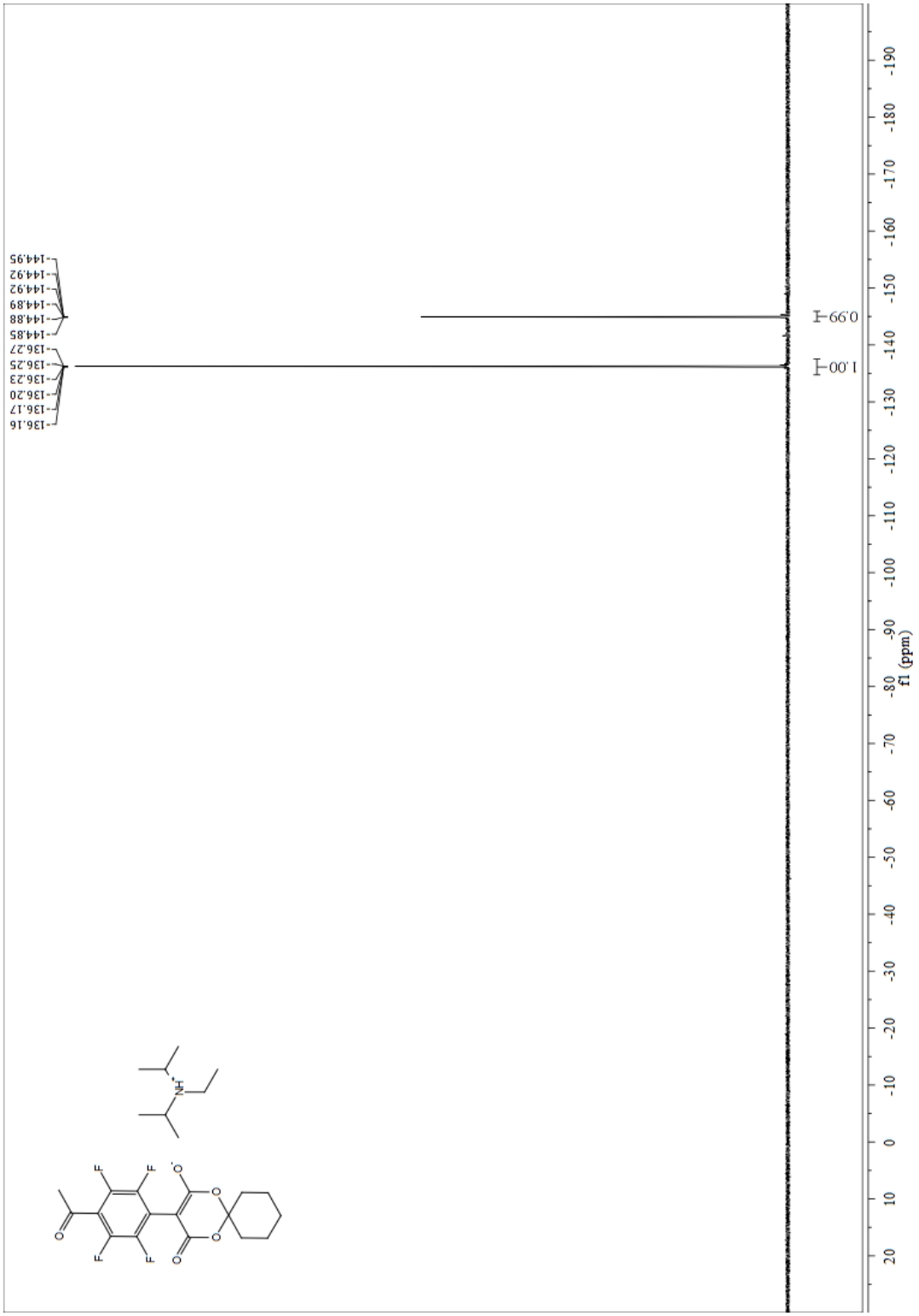
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4f (*N*-ethyl-*N*-isopropylpropan-2-aminium3-(2,3-difluoro-4-nitrophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



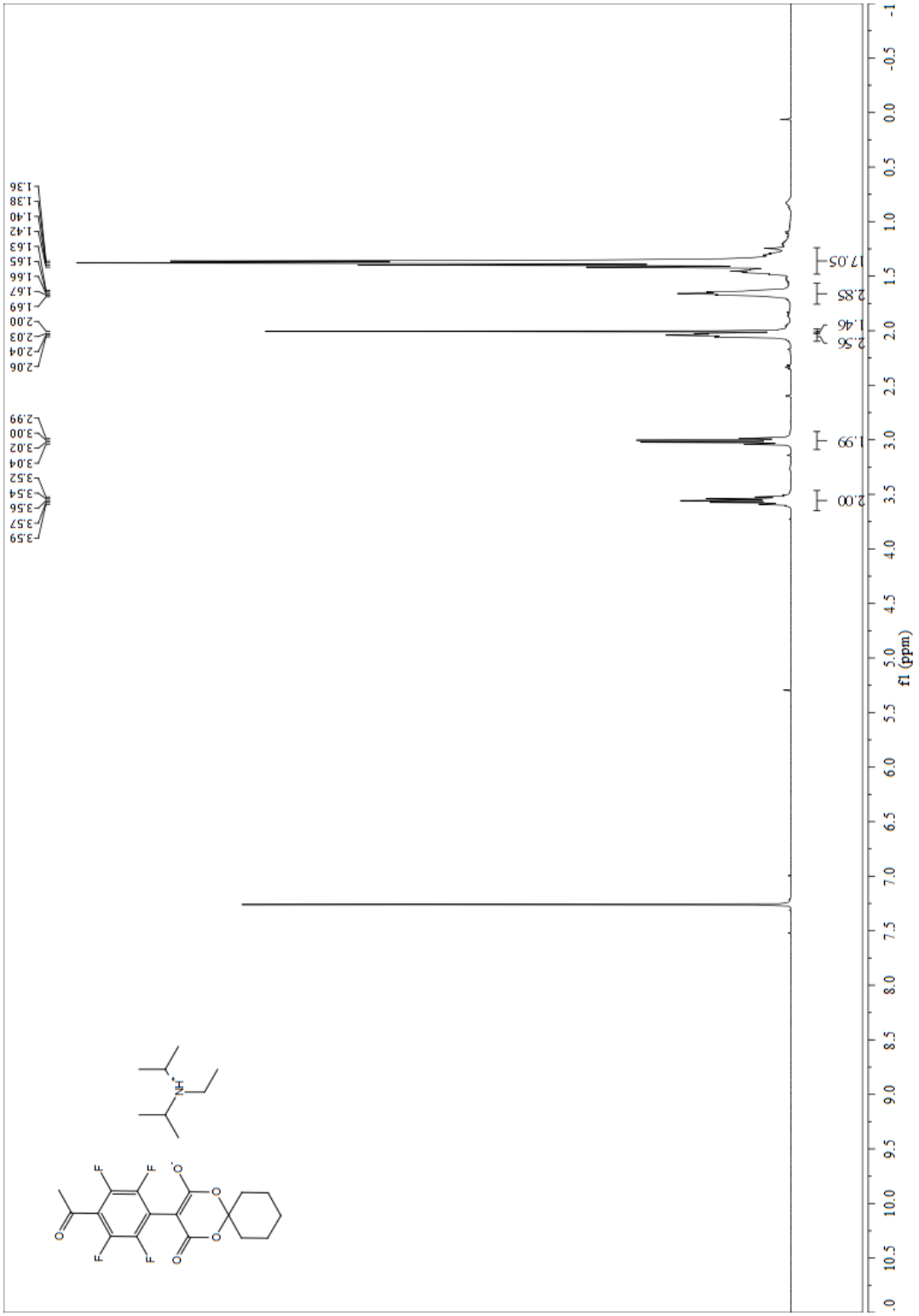
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4f (*N*-ethyl-*N*-isopropylpropan-2-aminium3-(2,3-difluoro-4-nitrophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



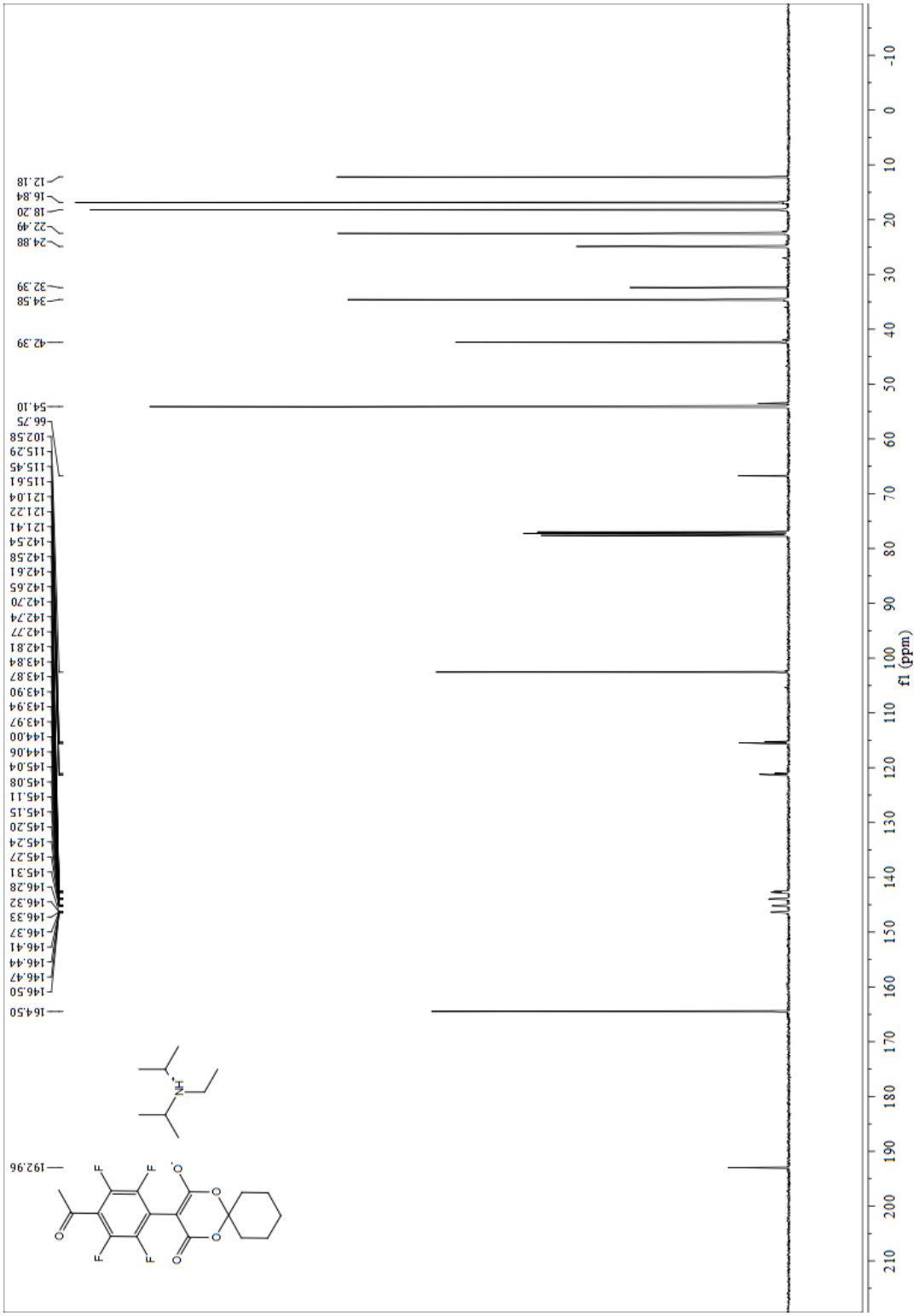
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4g (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-acetyl-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



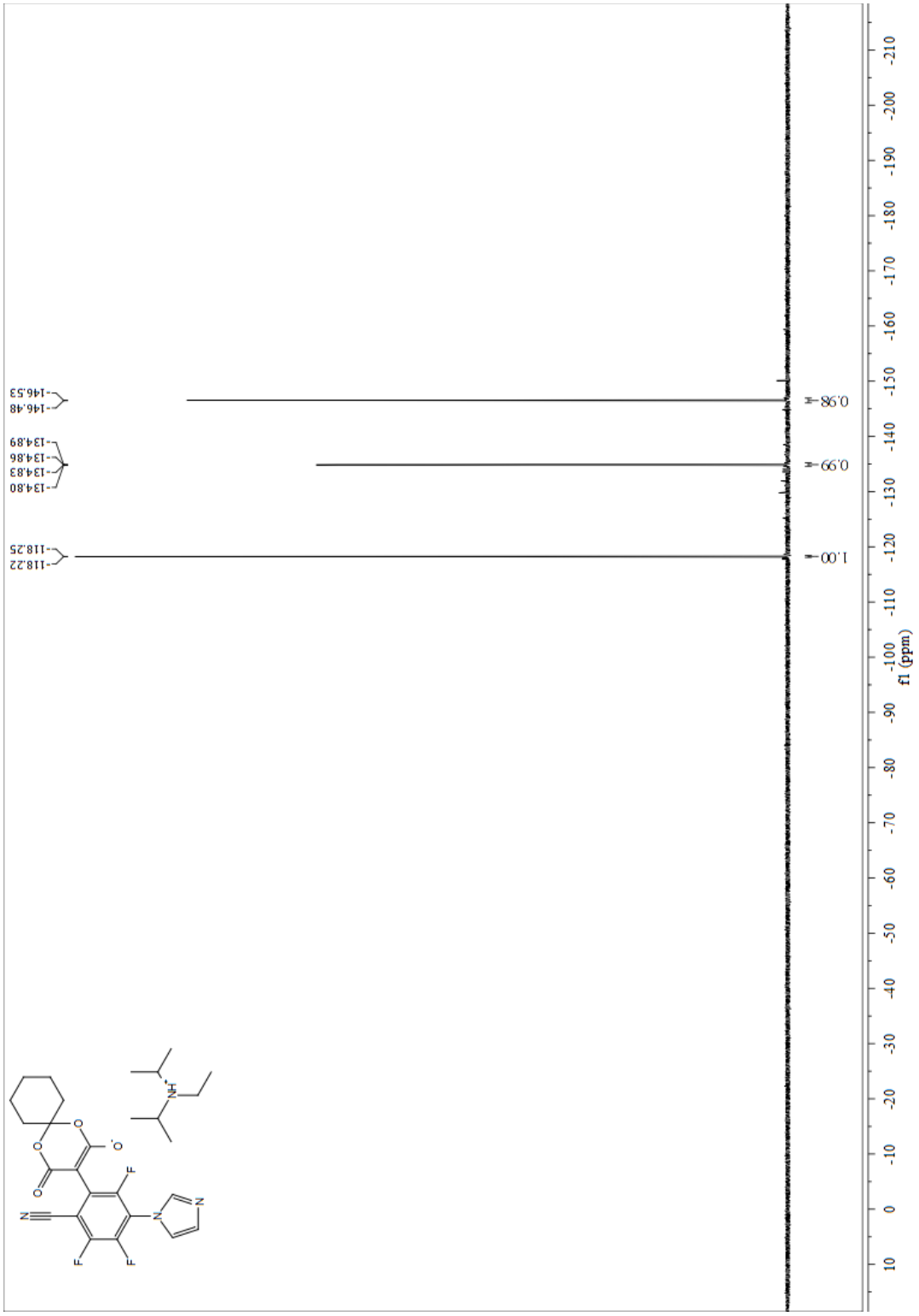
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4g (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-acetyl-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



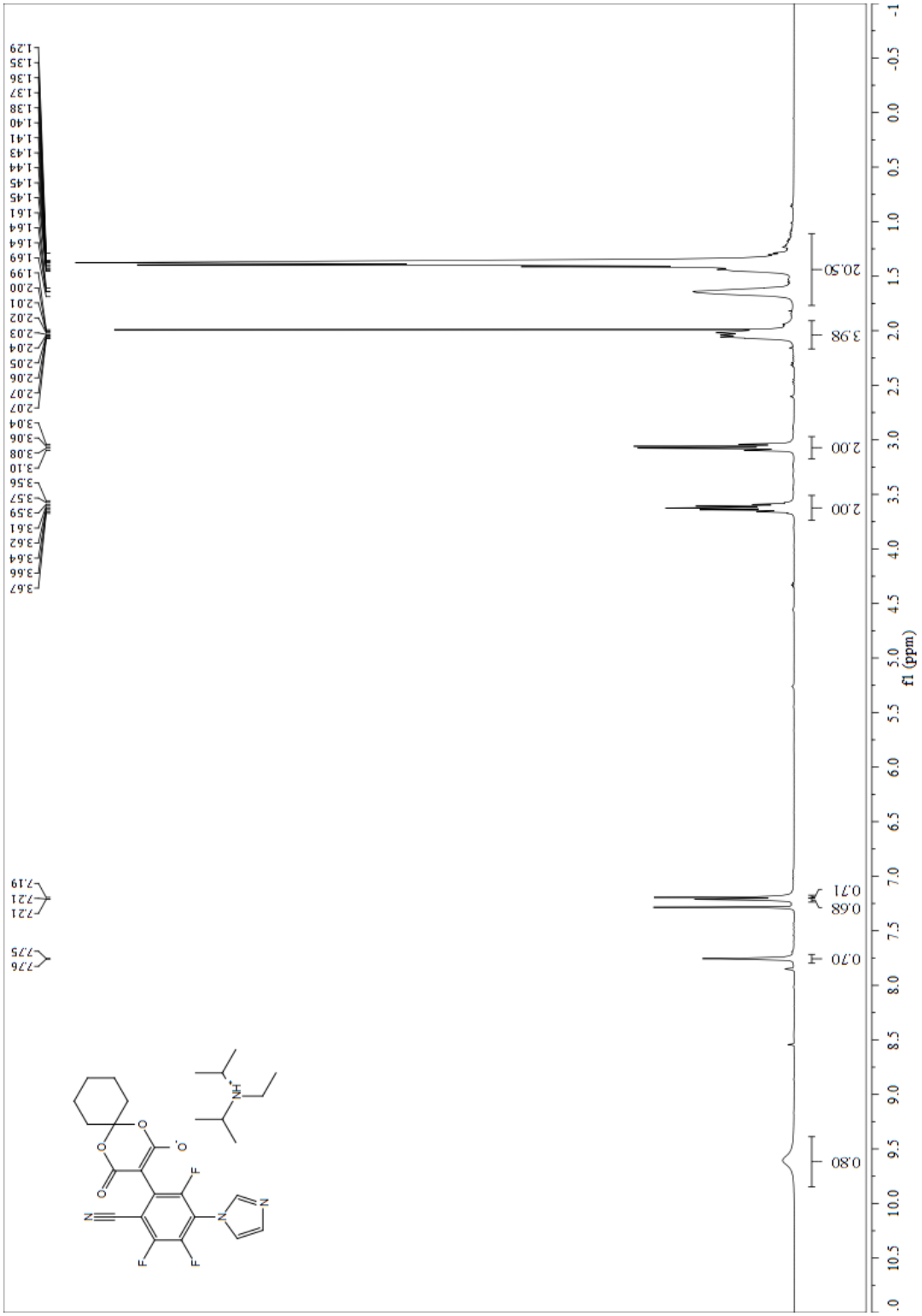
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4g (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-acetyl-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



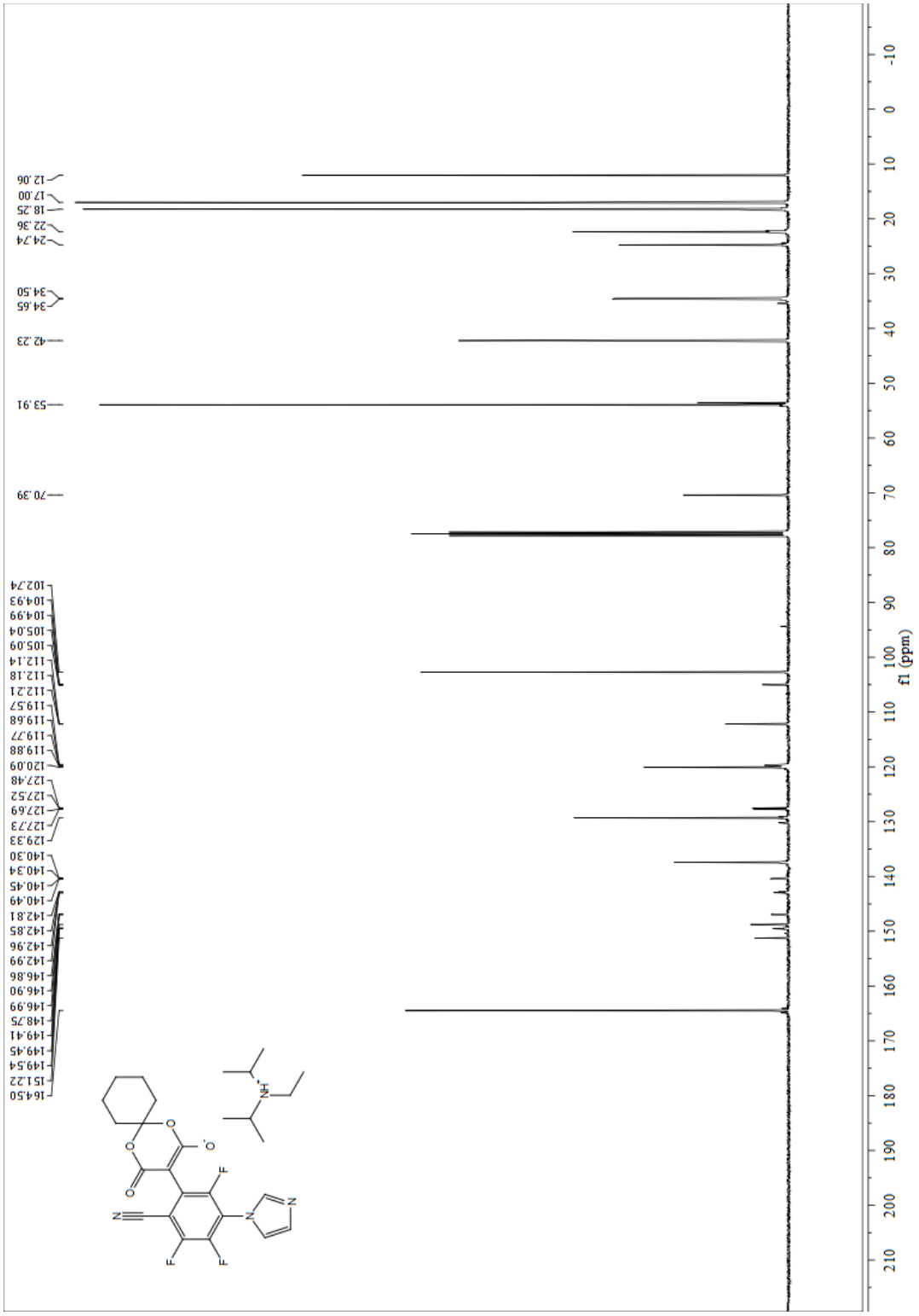
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4h (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(2-cyano-3,4,6-trifluoro-5-(1H-imidazol-1-yl)phenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



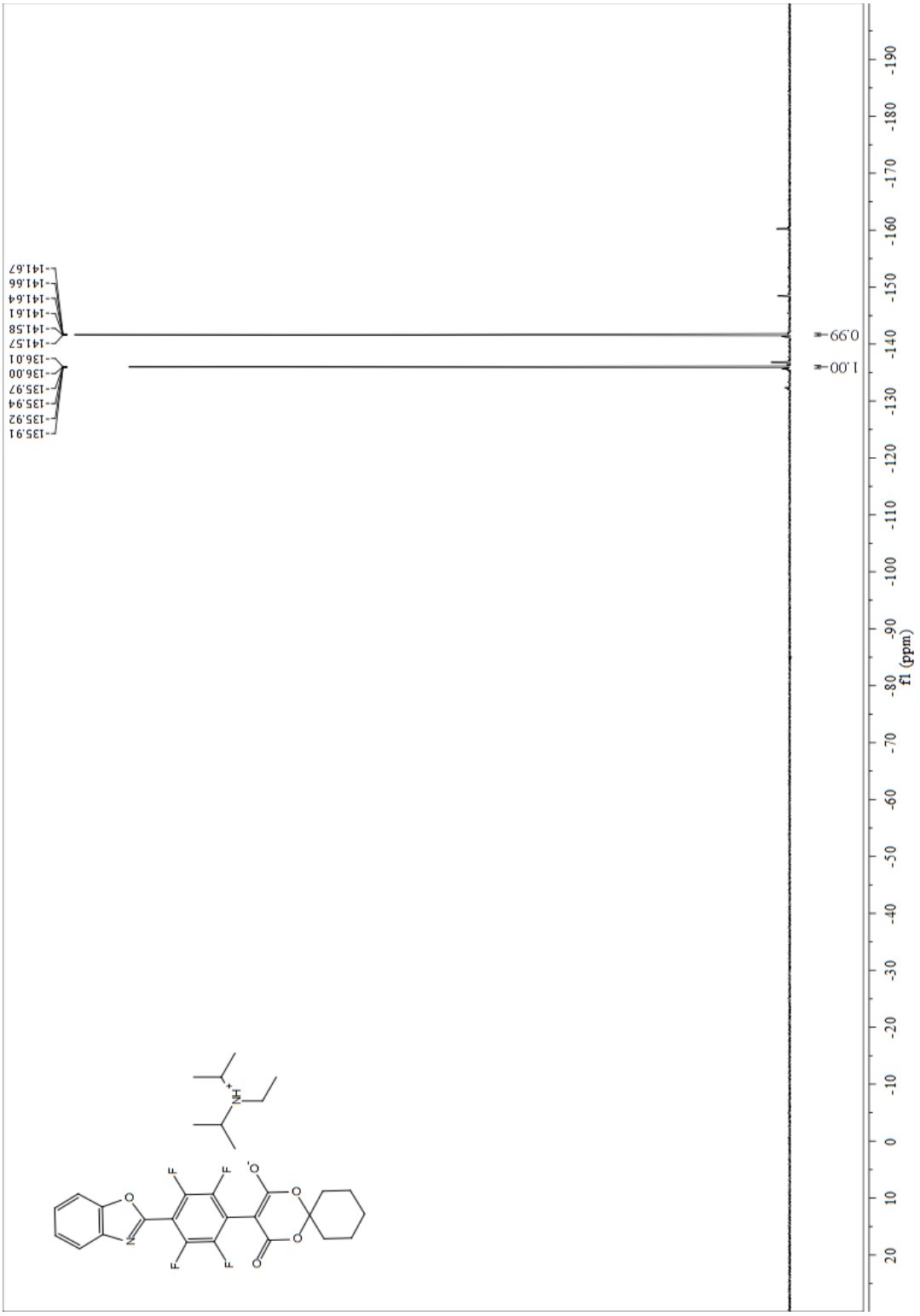
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4h (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(2-cyano-3,4,6-trifluoro-5-(1H-imidazol-1-yl)phenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



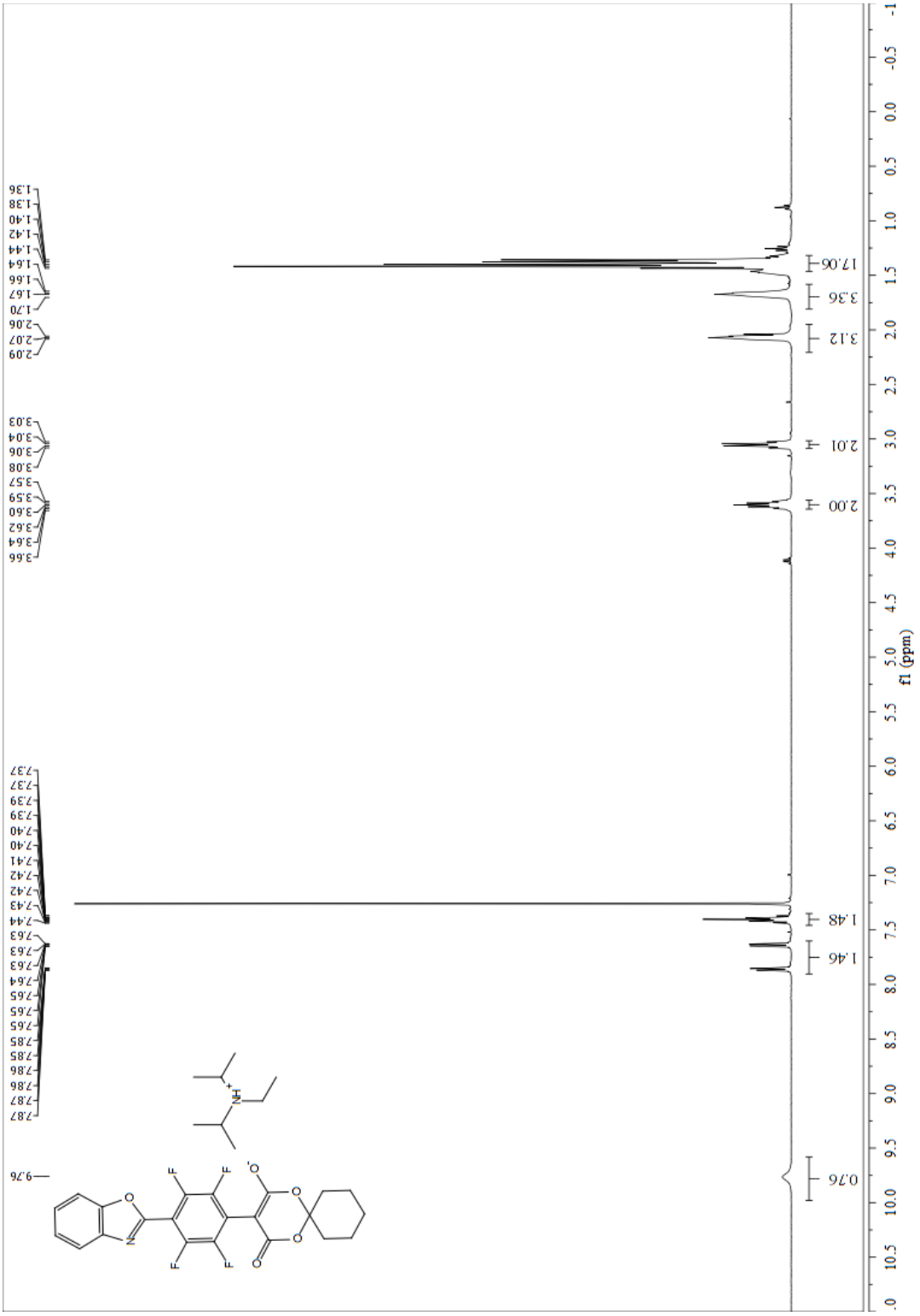
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4h (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(2-cyano-3,4,6-trifluoro-5-(1H-imidazol-1-yl)phenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



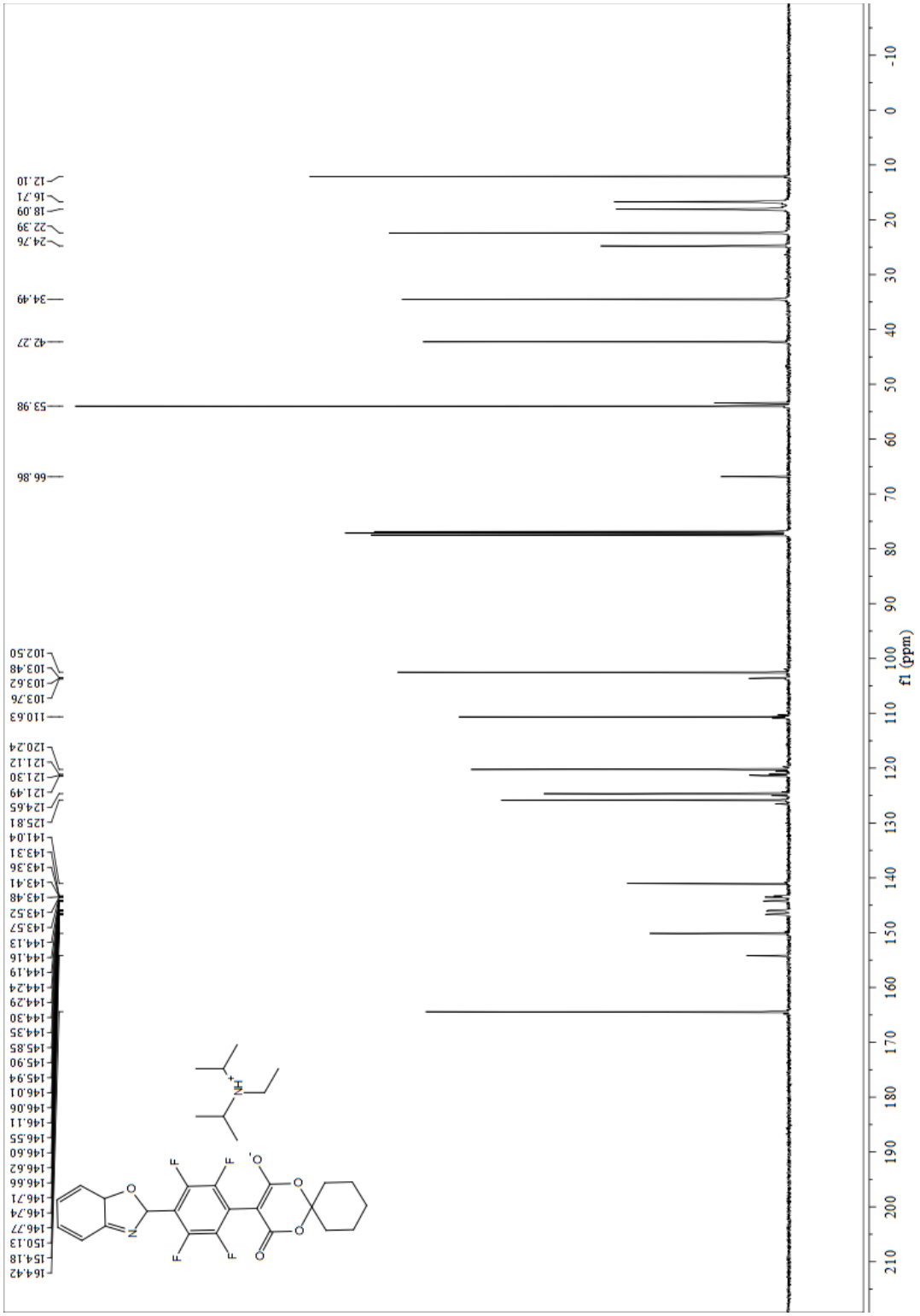
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4i (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-(2,7a-dihydrobenzo[d]oxazol-2-yl)-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



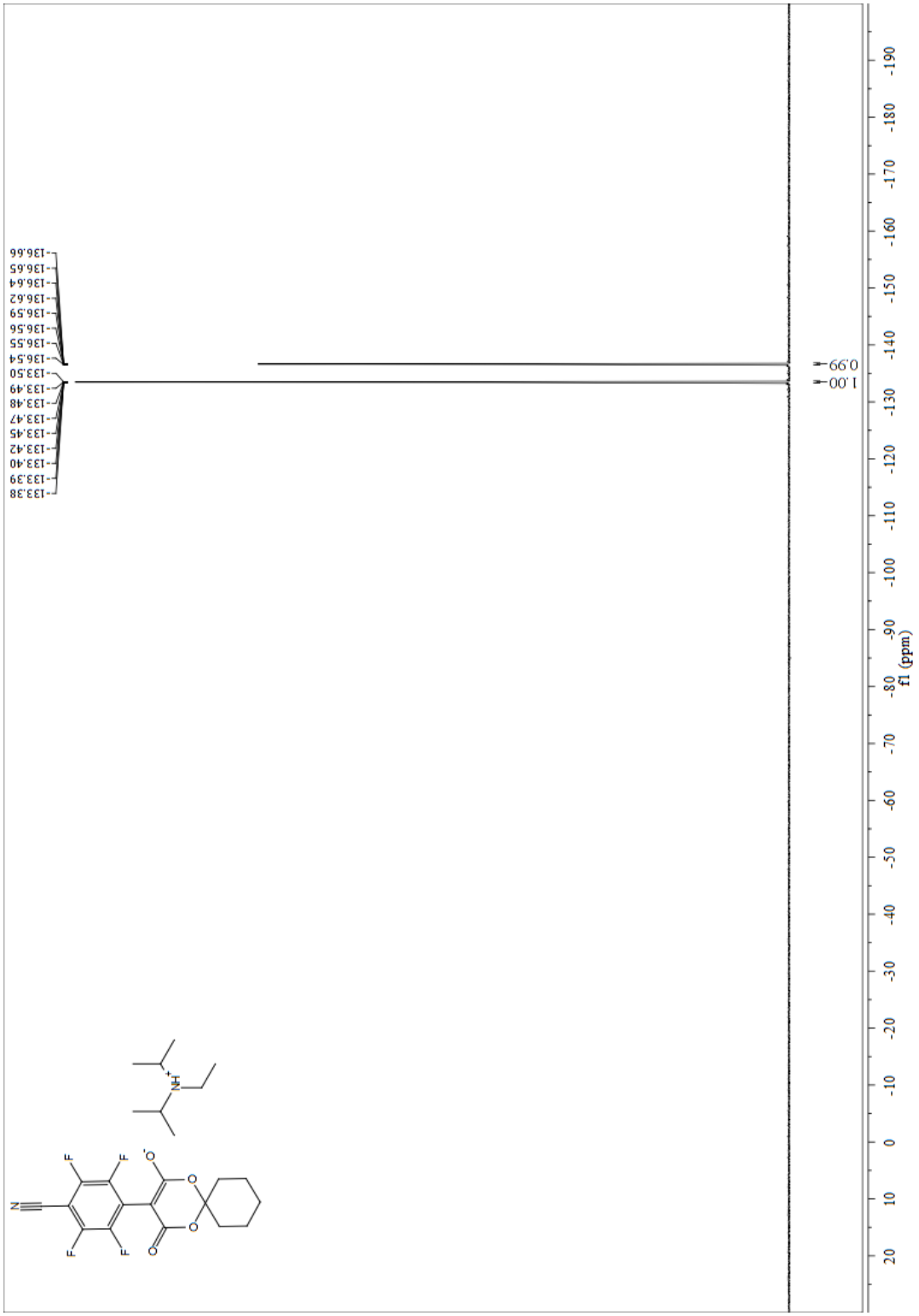
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4i (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-(2,7a-dihydrobenzo[d]oxazol-2-yl)-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



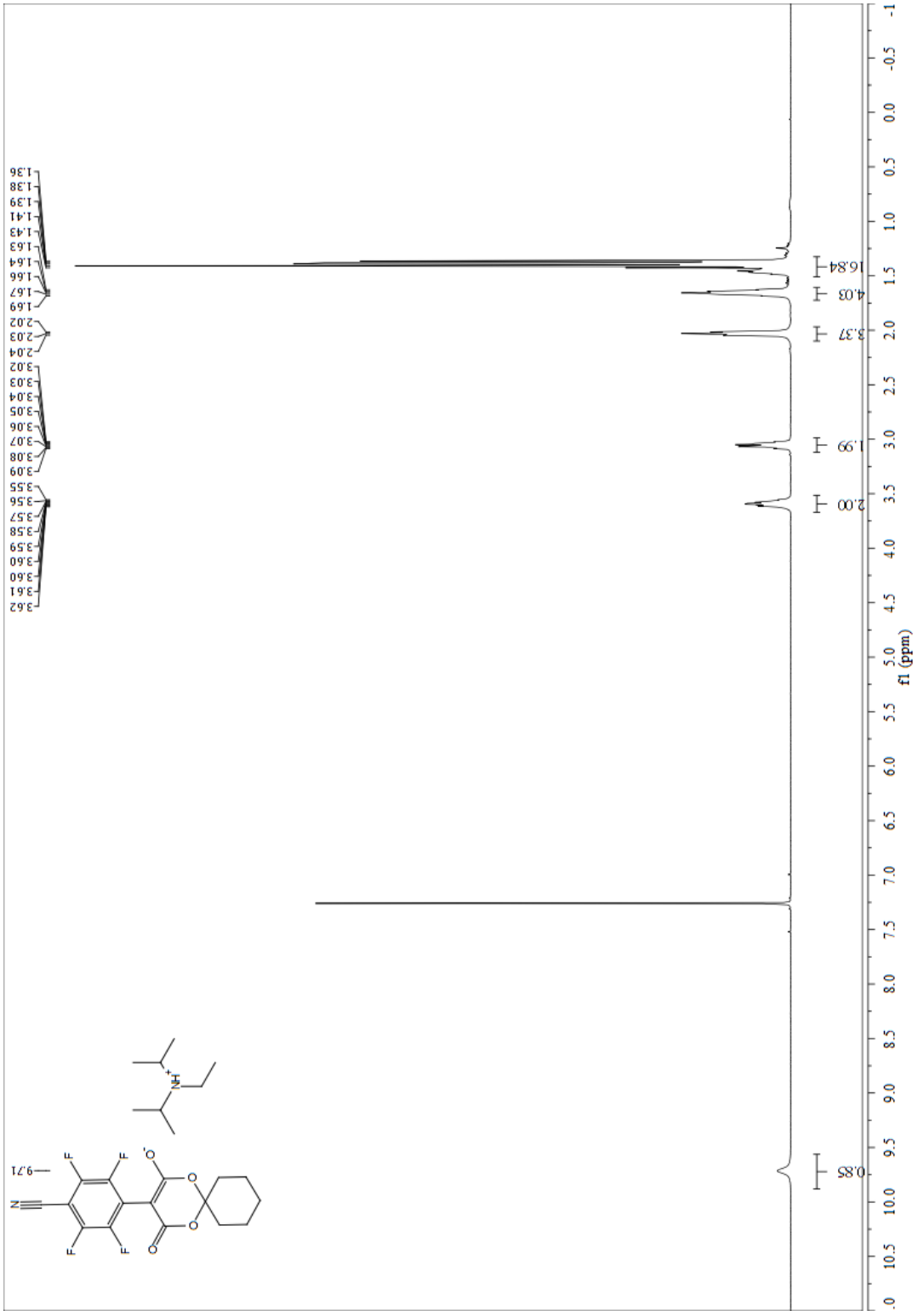
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4i (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-(2,7a-dihydrobenzo[d]oxazol-2-yl)-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



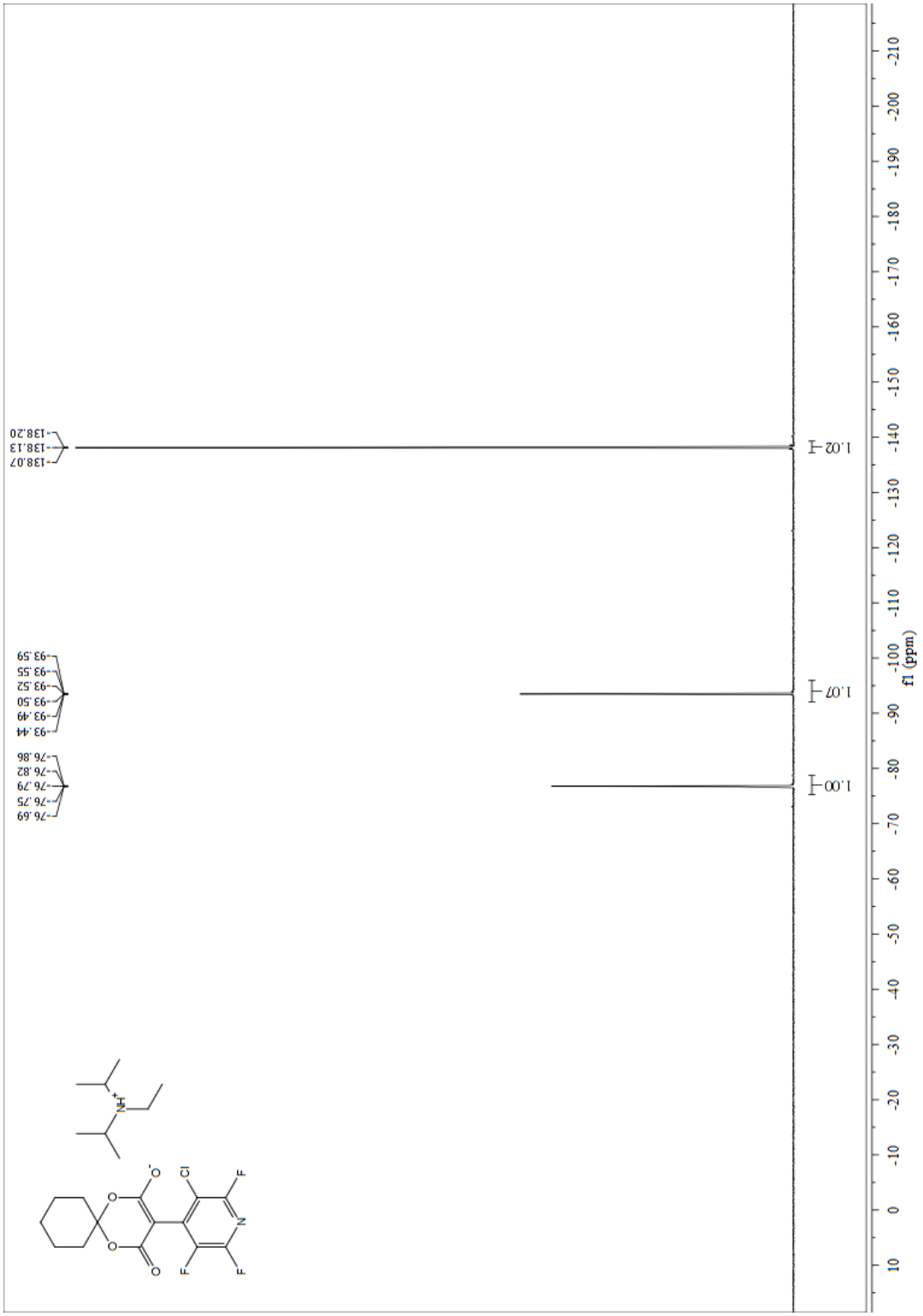
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4j (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-cyano-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



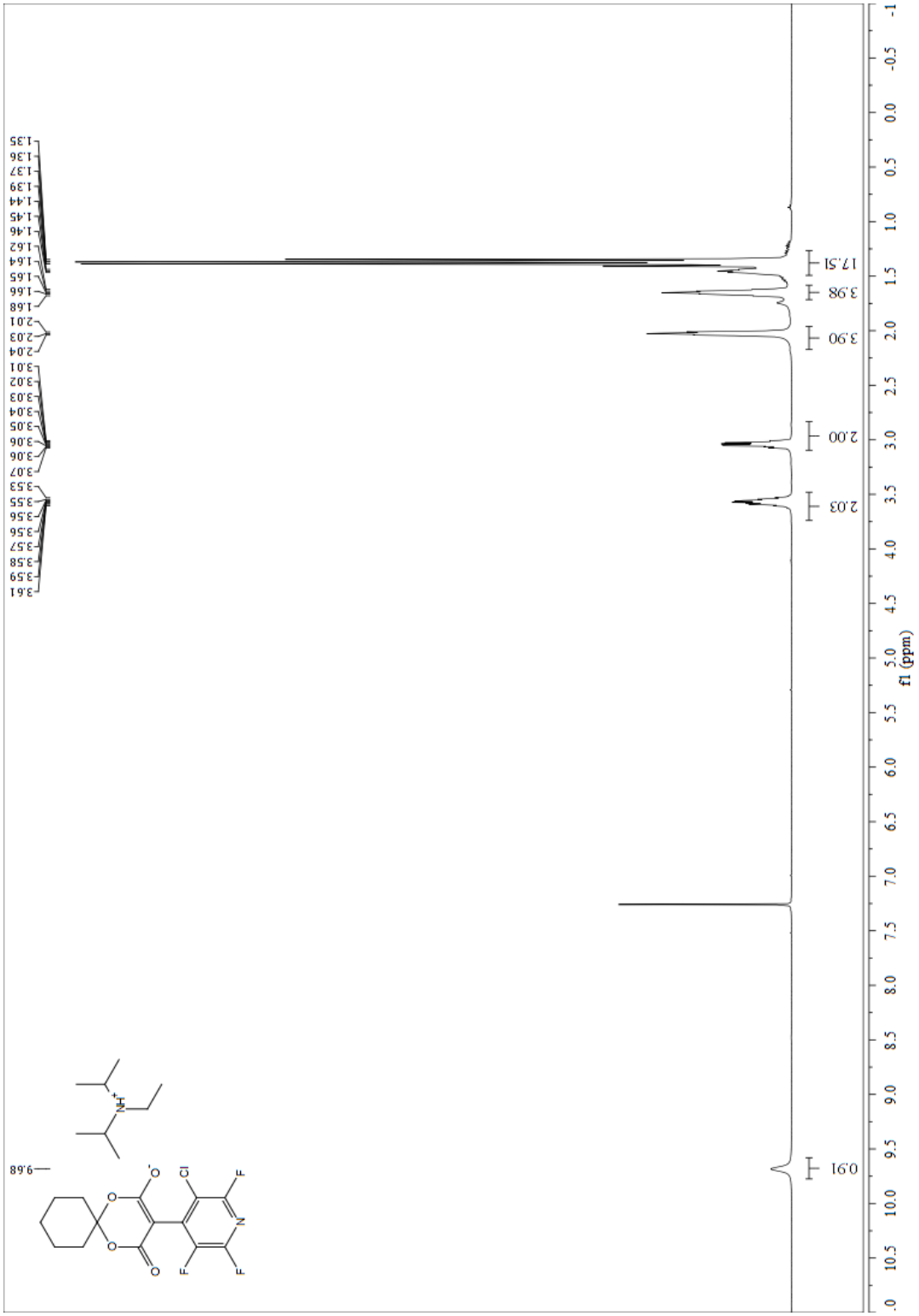
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4j (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(4-cyano-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



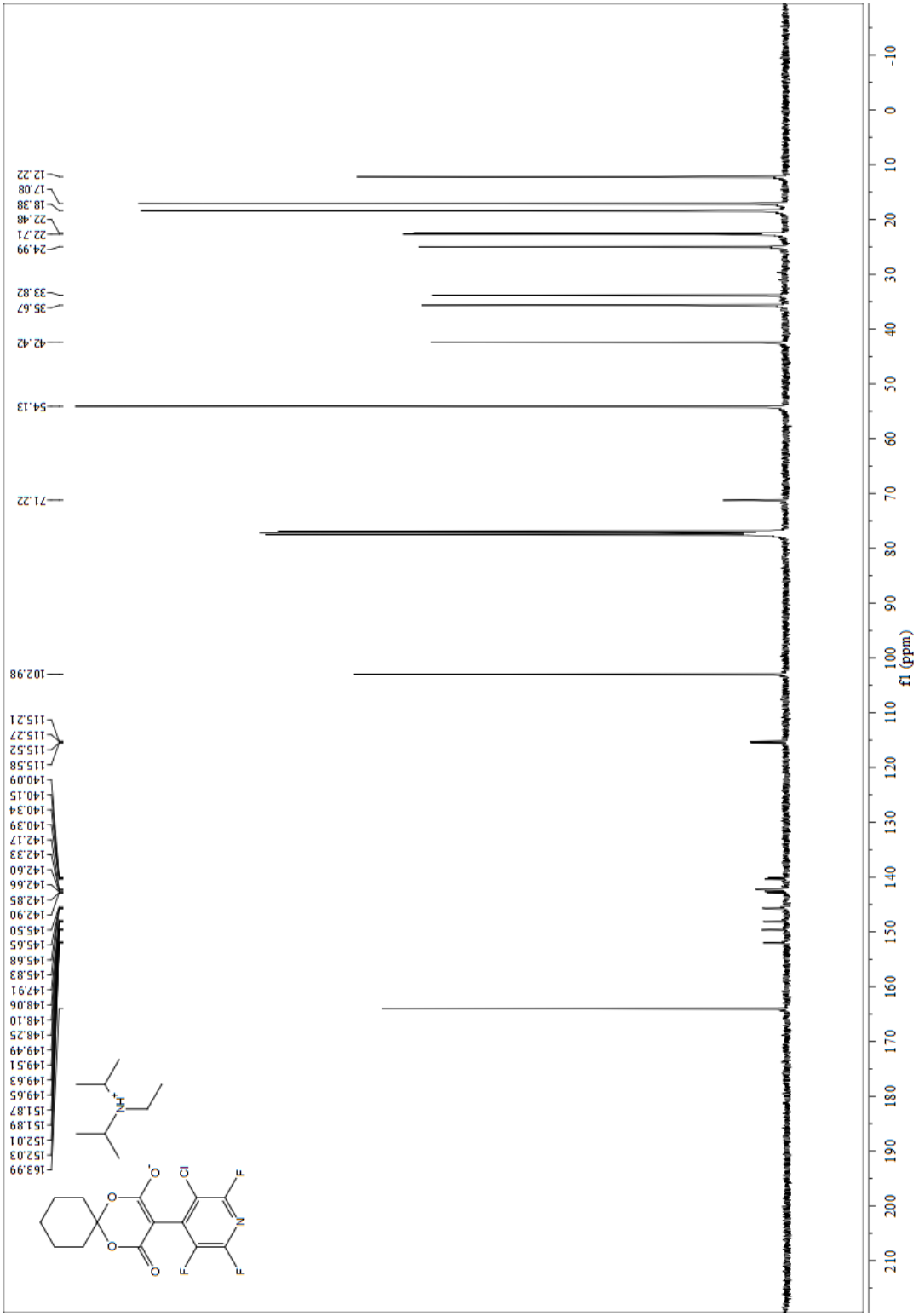
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4k (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(3-chloro-2,5,6-trifluoropyridin-4-yl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



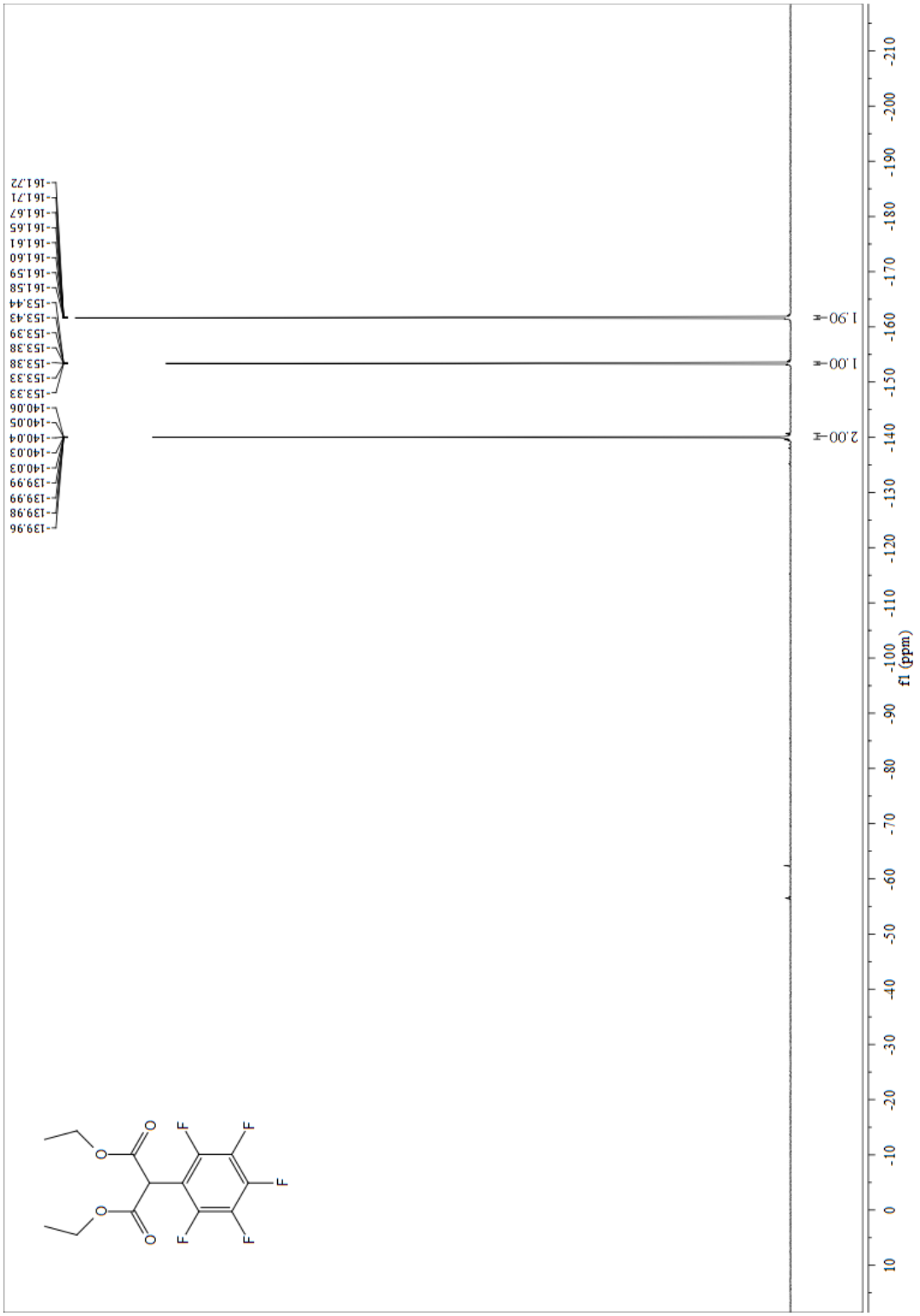
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4k (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(3-chloro-2,5,6-trifluoropyridin-4-yl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



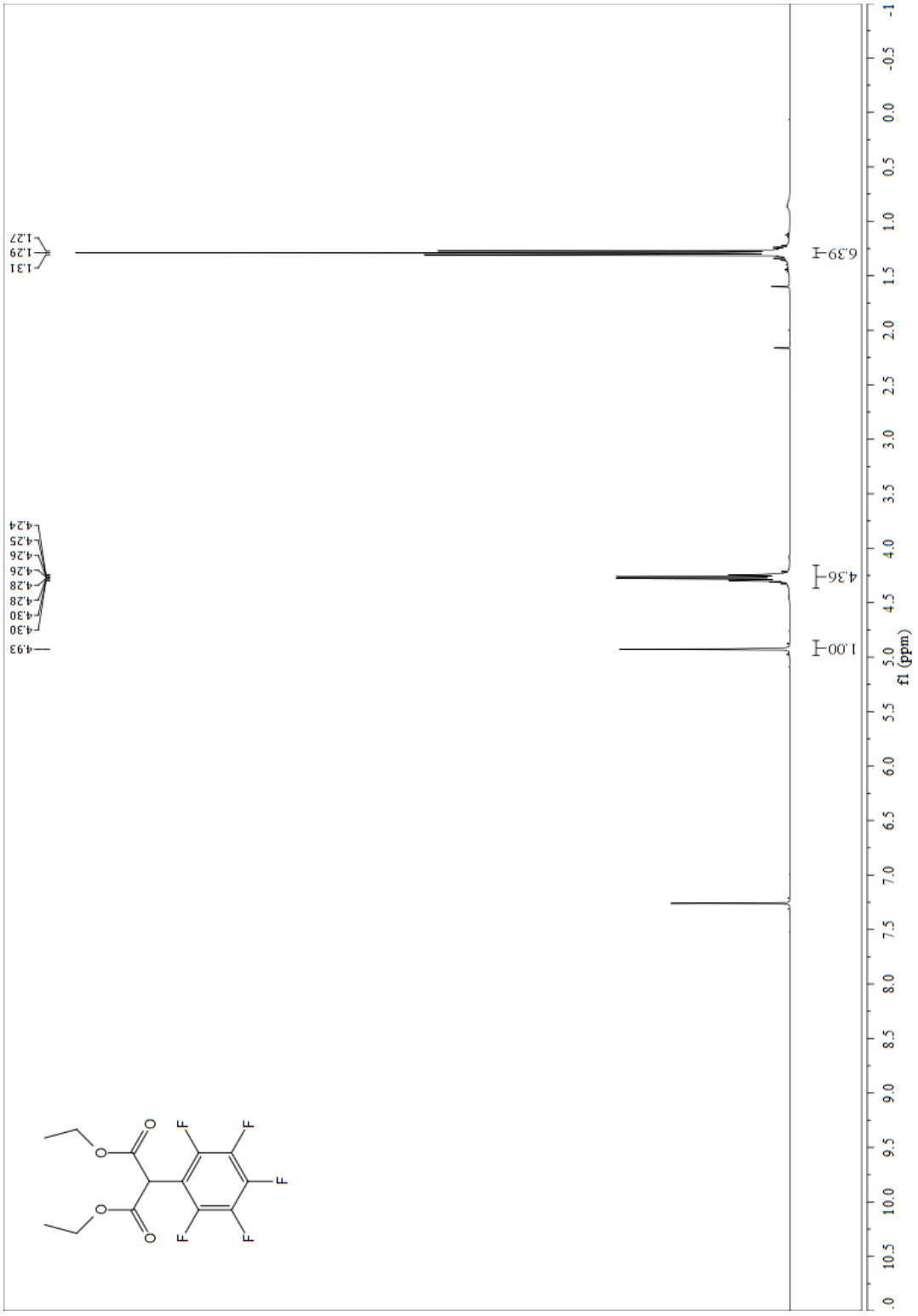
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.4k (*N*-ethyl-*N*-isopropylpropan-2-aminium 3-(3-chloro-2,5,6-trifluoropyridin-4-yl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate)



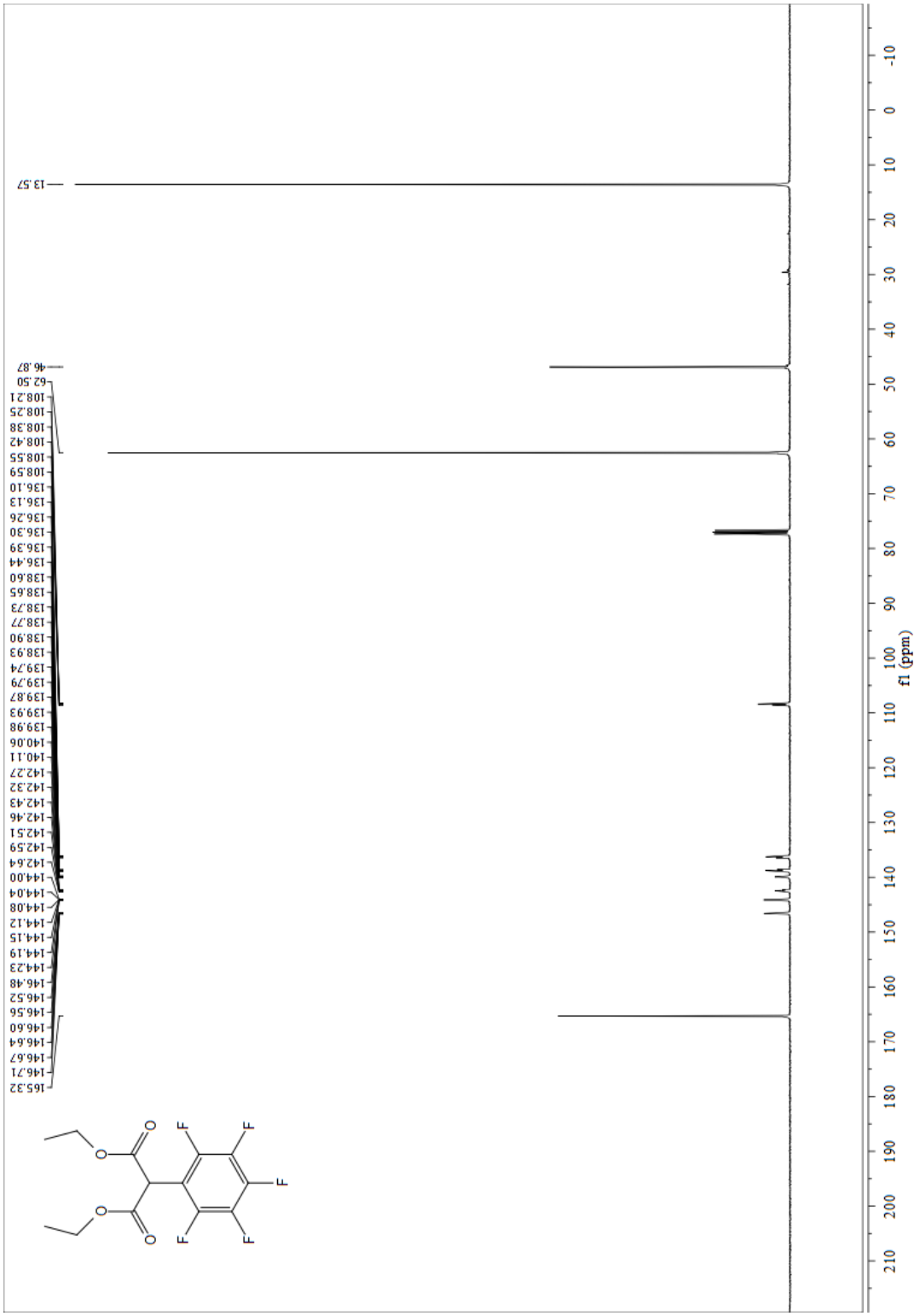
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5a (Diethyl 2-(perfluorophenyl)malonate)



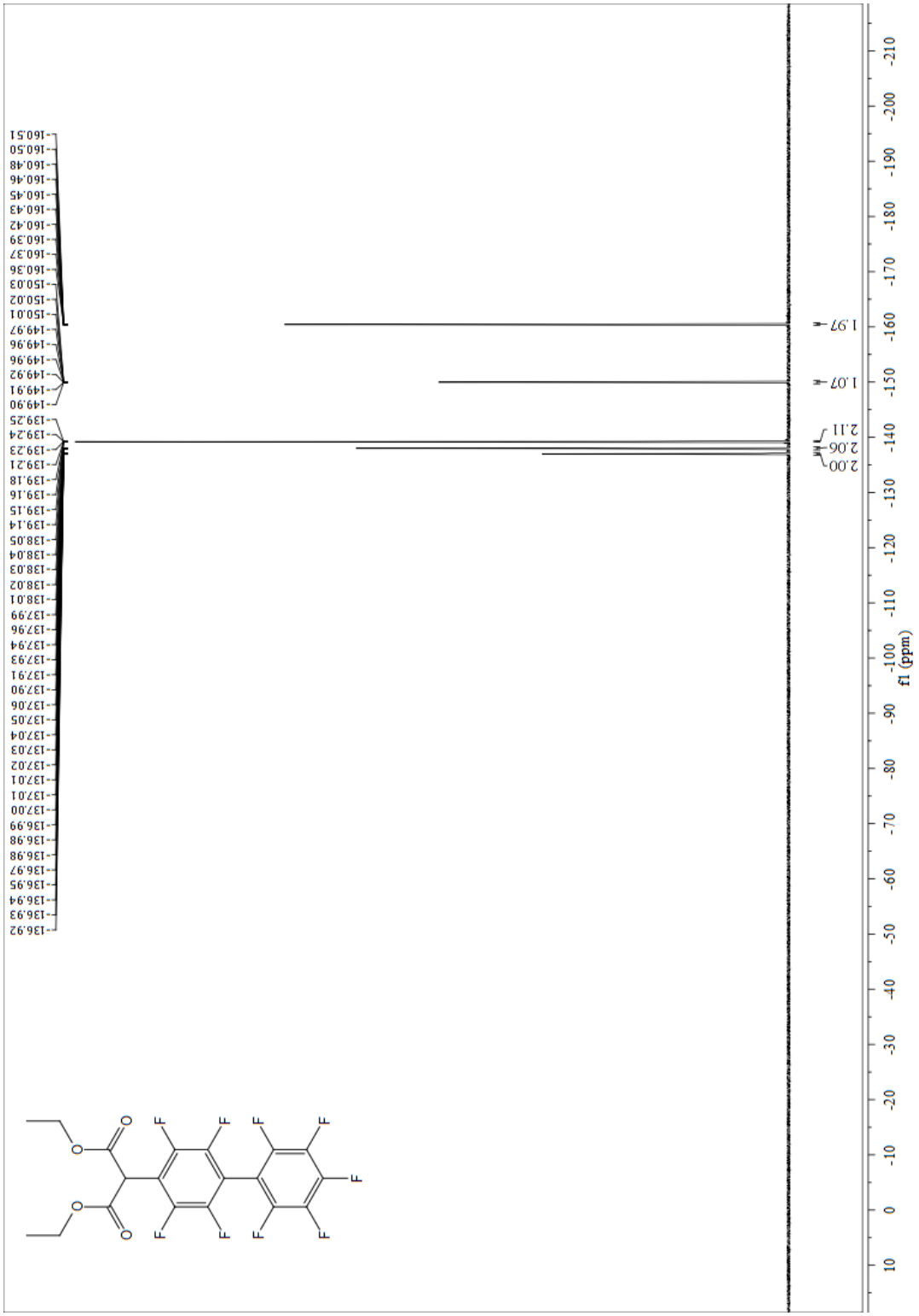
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5a (Diethyl 2-(perfluorophenyl)malonate)



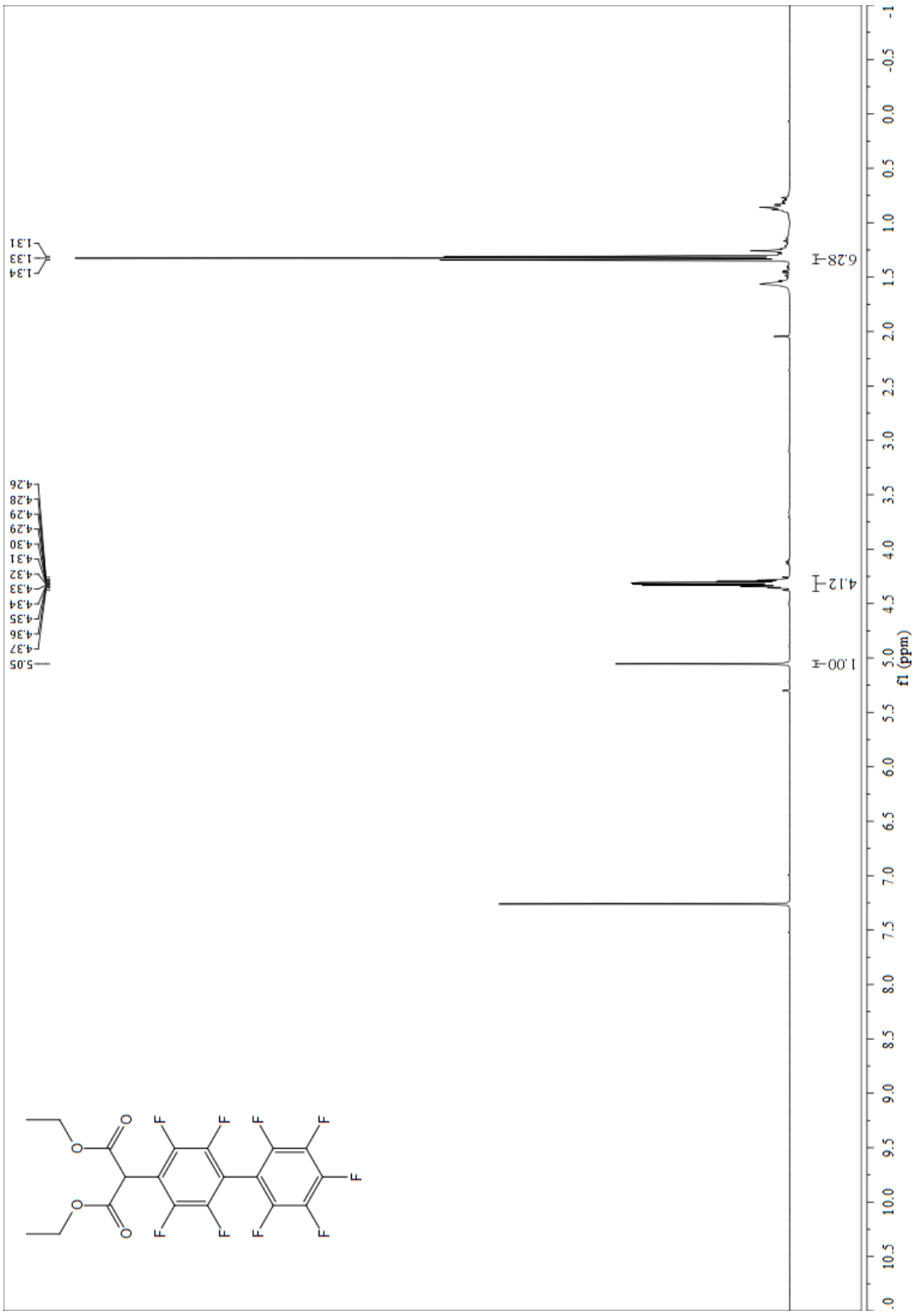
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5a (Diethyl 2-(perfluorophenyl)malonate)



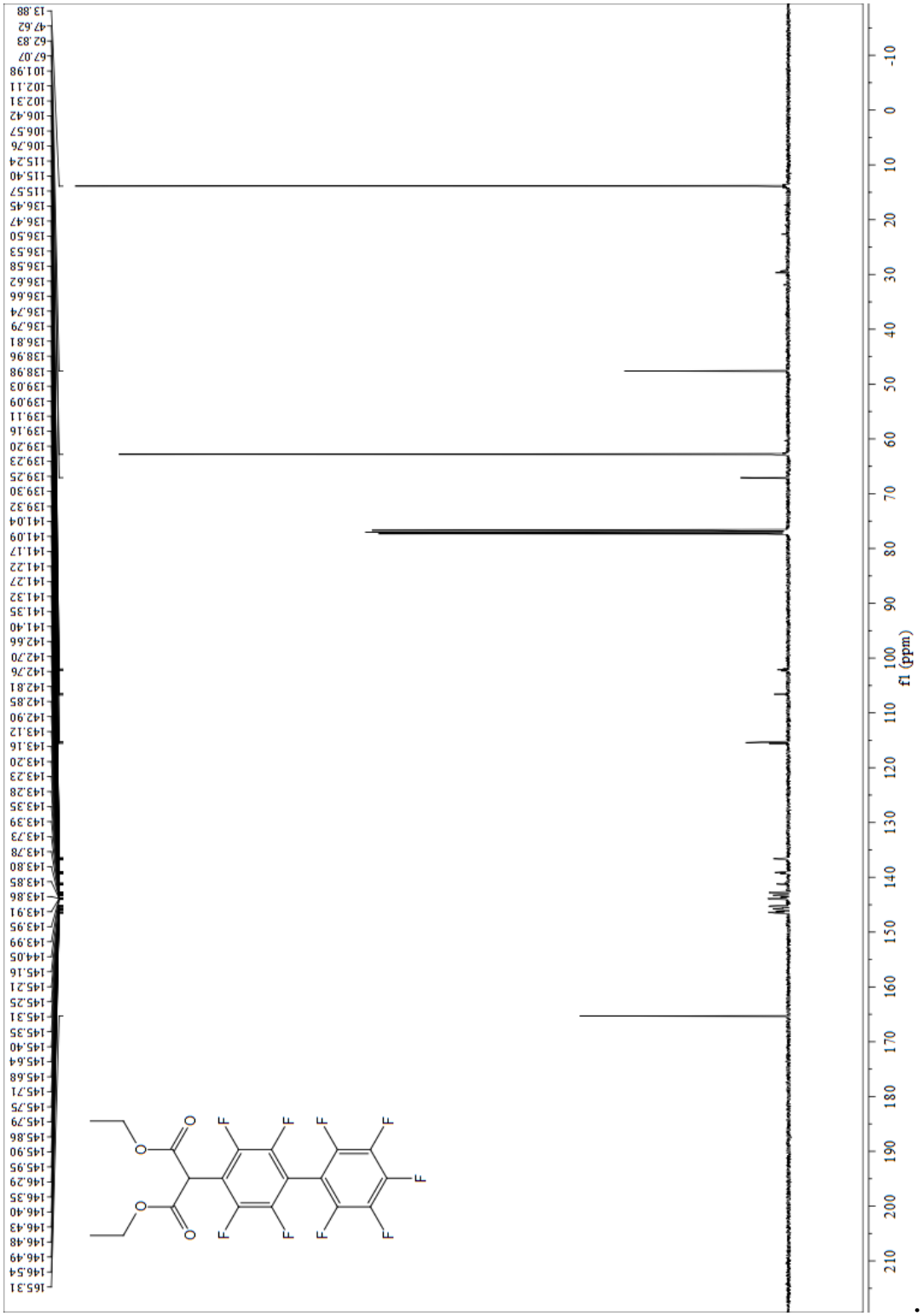
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5b (Diethyl 2-(perfluoro-[1,1'-biphenyl]-4-yl)malonate)



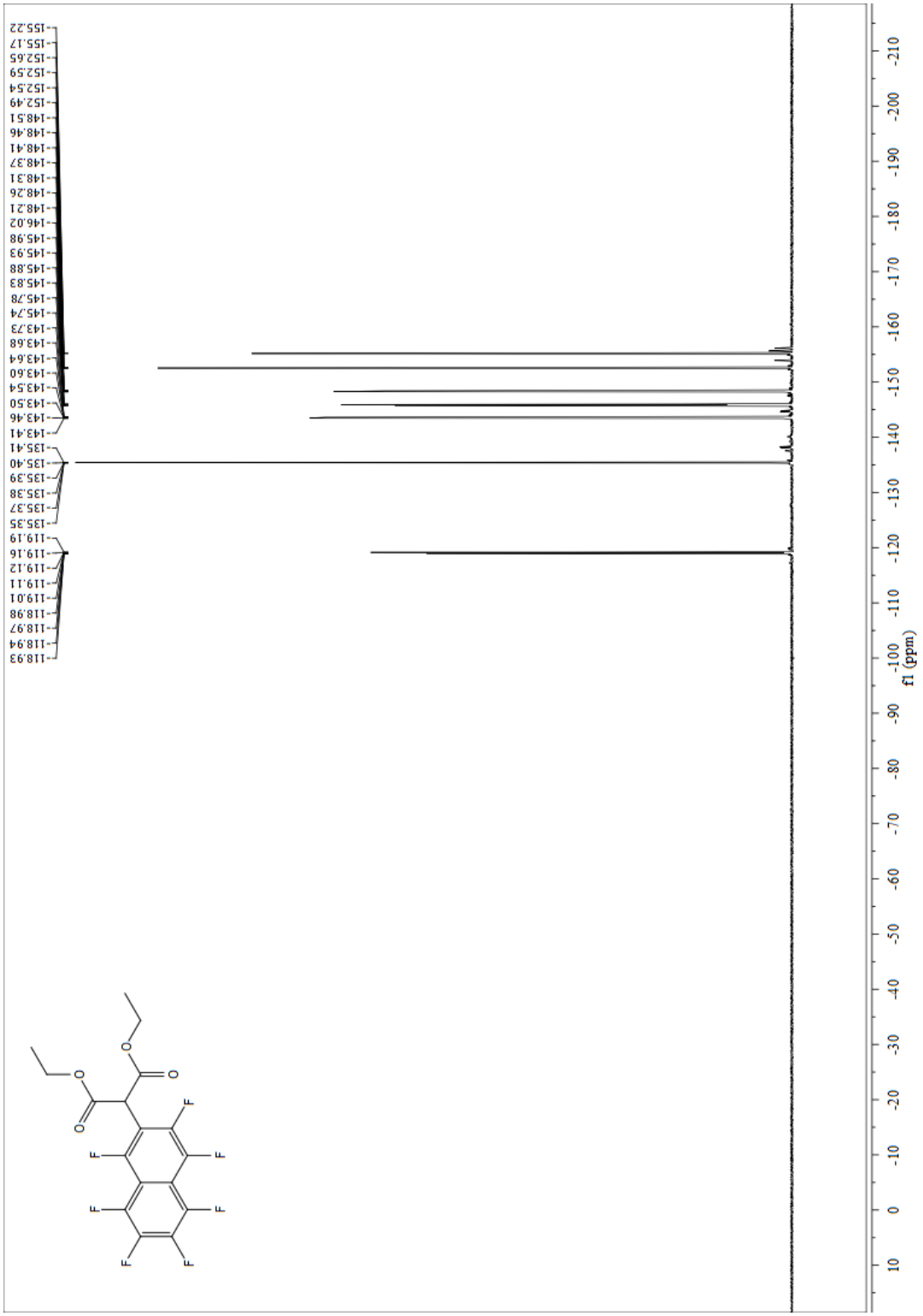
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5b (Diethyl 2-(perfluoro-[1,1'-biphenyl]-4-yl)malonate)



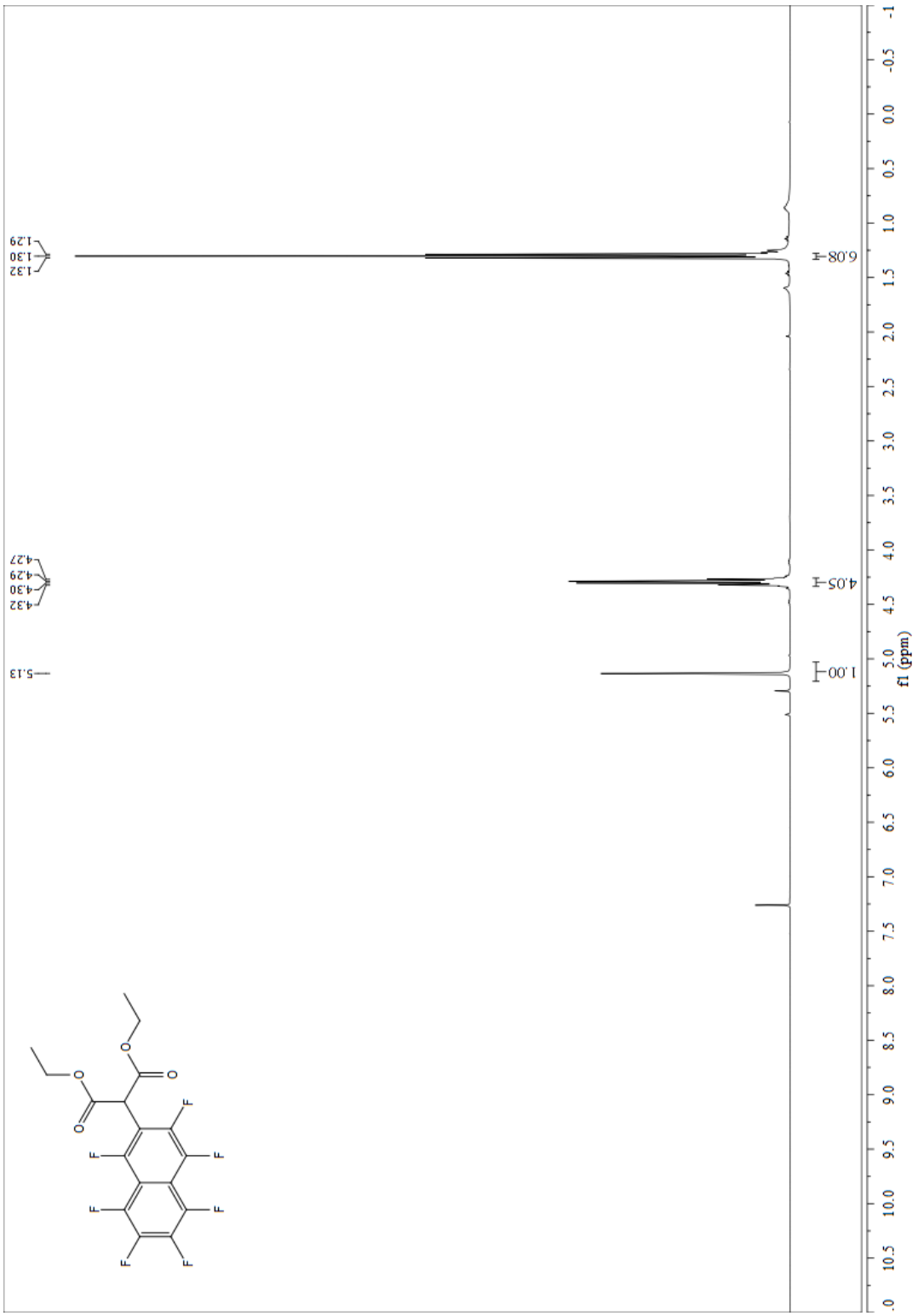
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5b (Diethyl 2-(perfluoro-[1,1'-biphenyl]-4-yl)malonate)



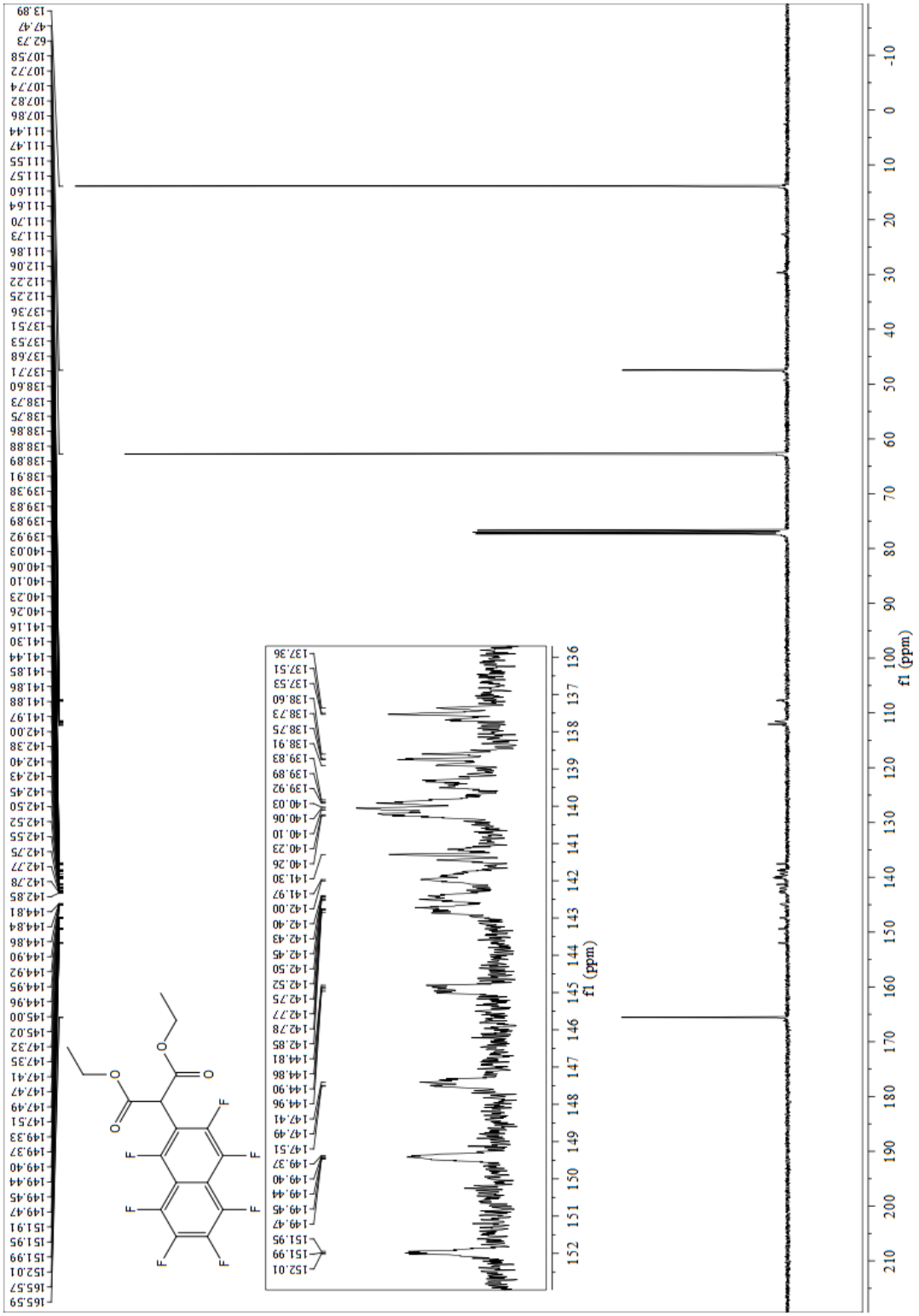
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5c (Diethyl 2-(perfluoronaphthalen-2-yl)malonate)



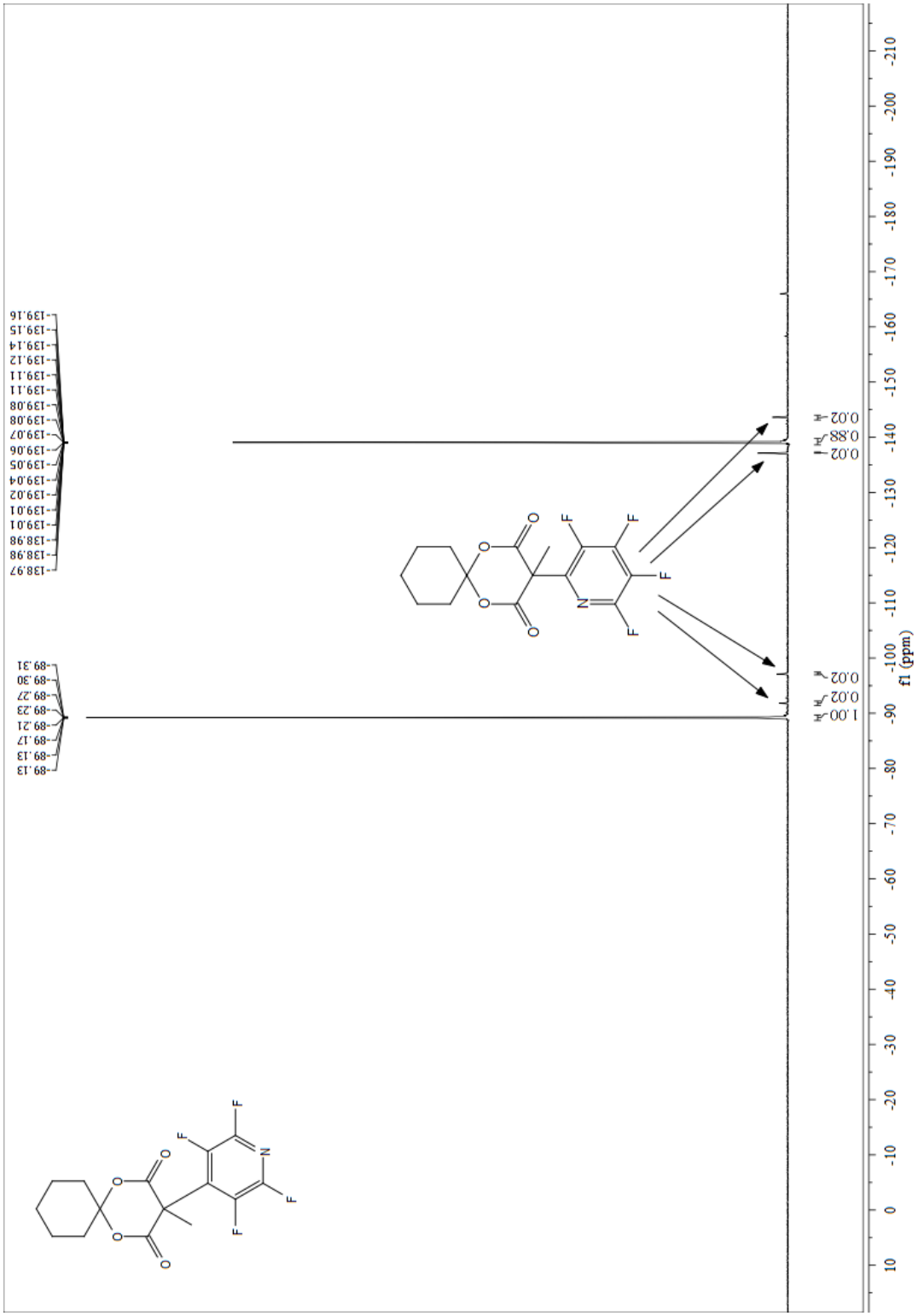
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5c (Diethyl 2-(perfluoronaphthalen-2-yl)malonate)



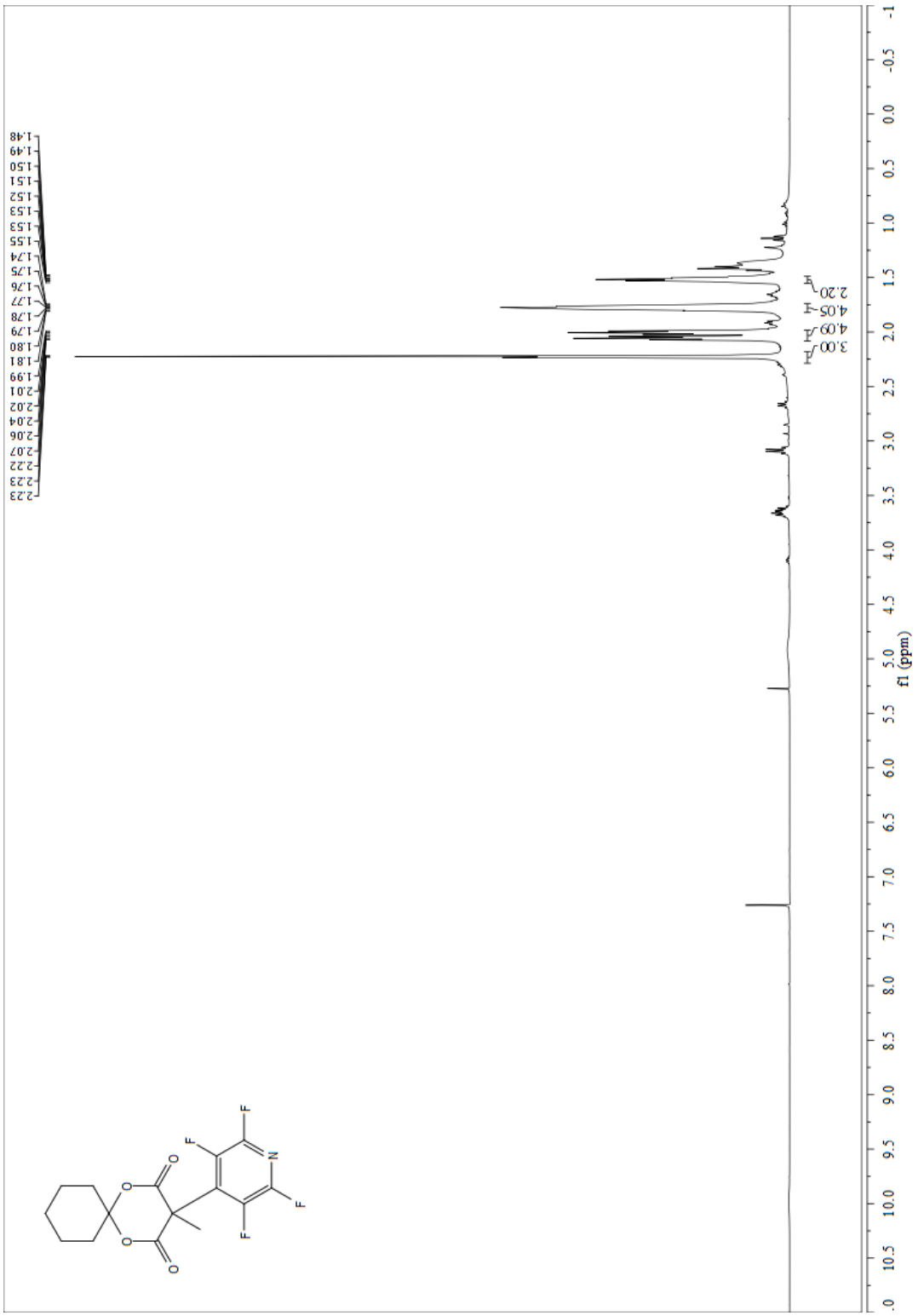
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.5c (Diethyl 2-(perfluoronaphthalen-2-yl)malonate)



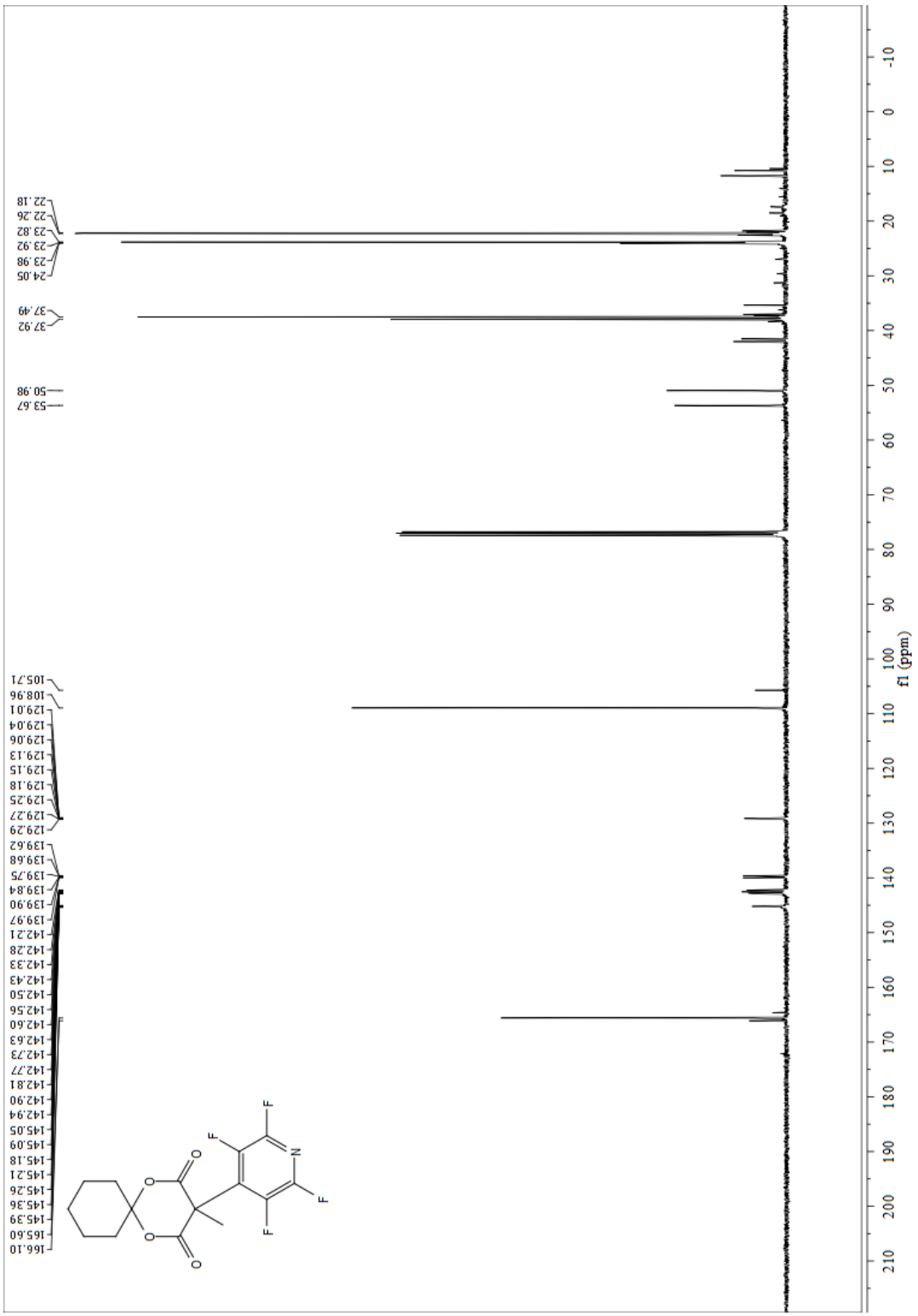
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7a (3-methyl-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



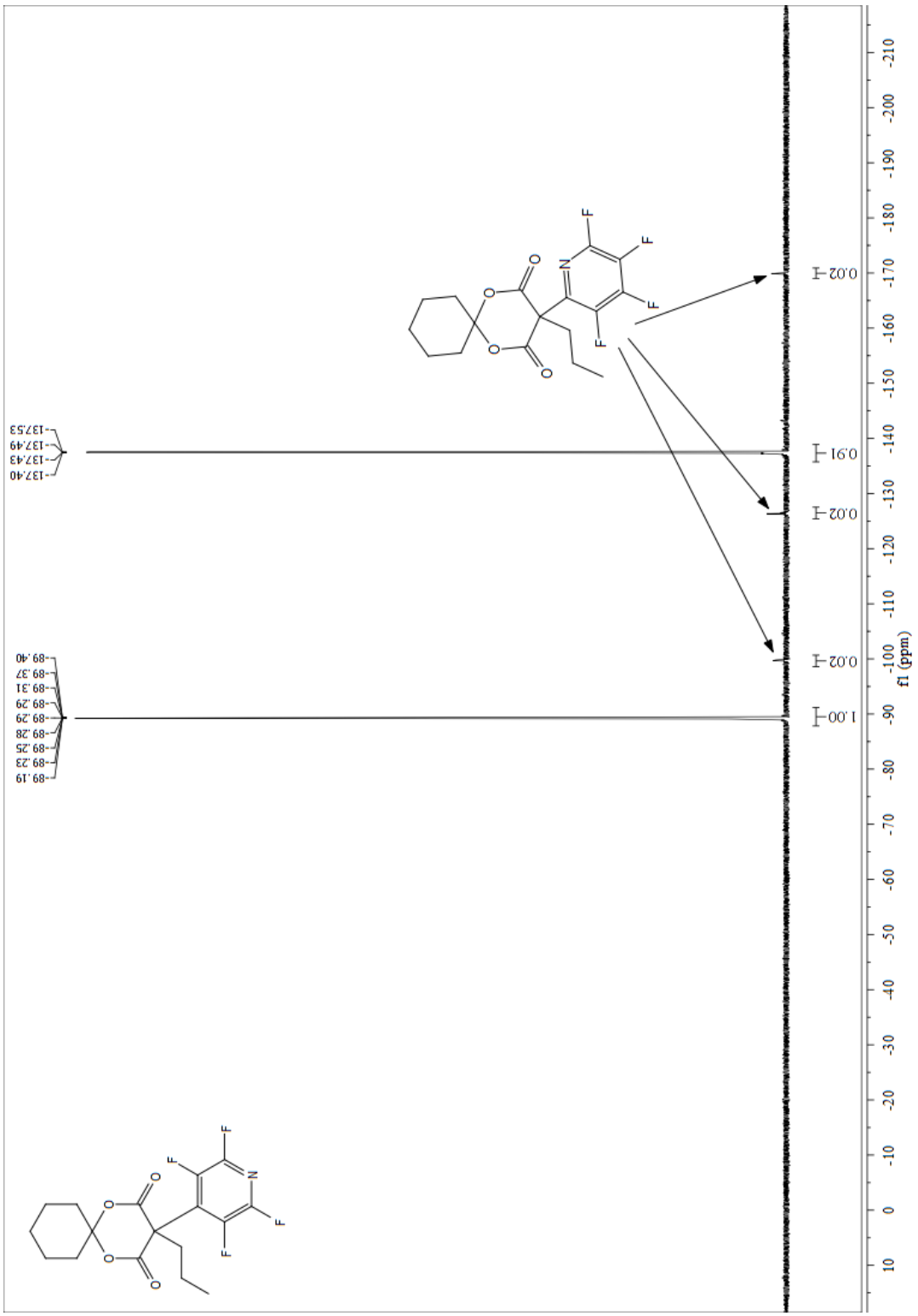
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7a (3-methyl-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



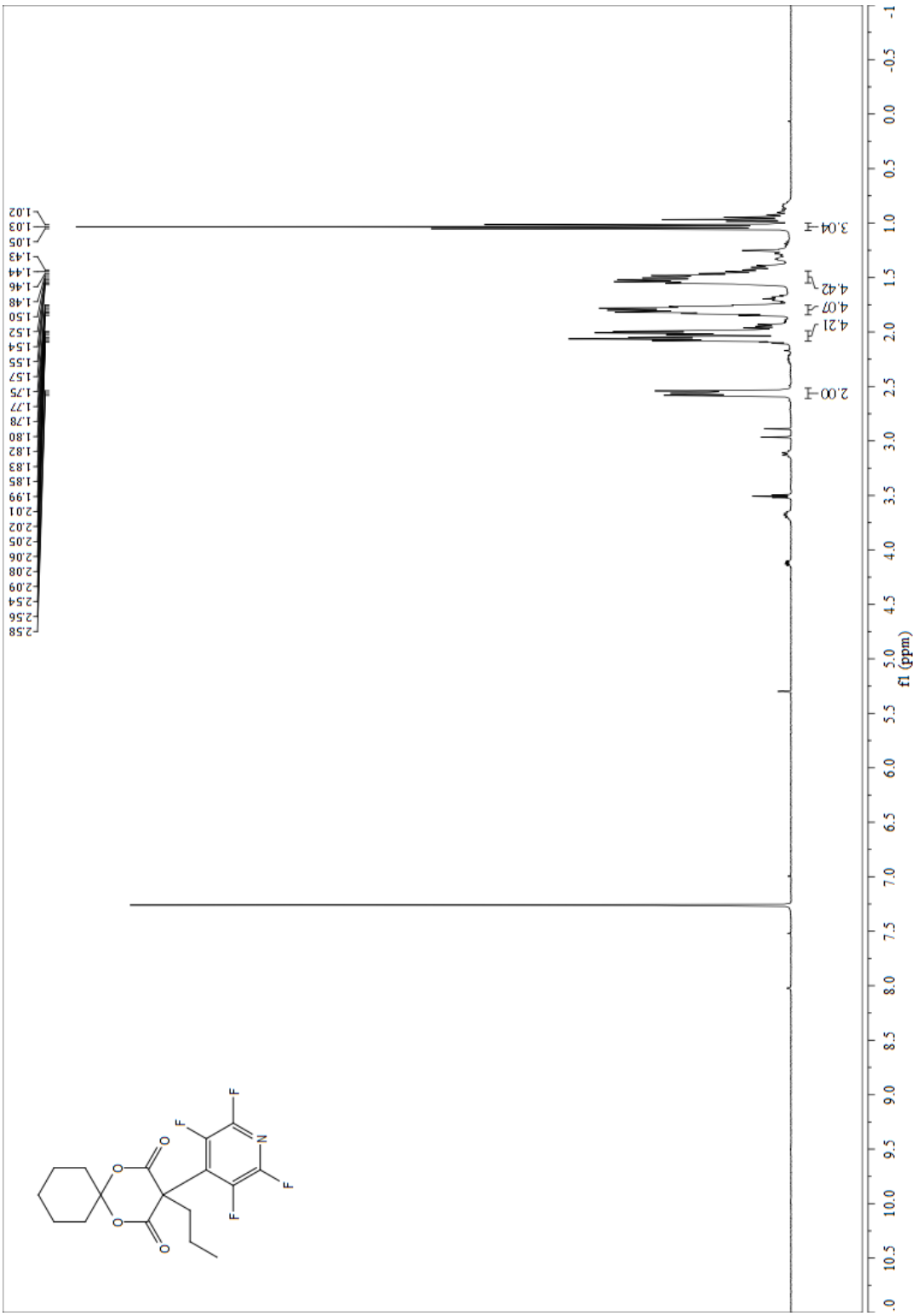
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7a (3-methyl-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



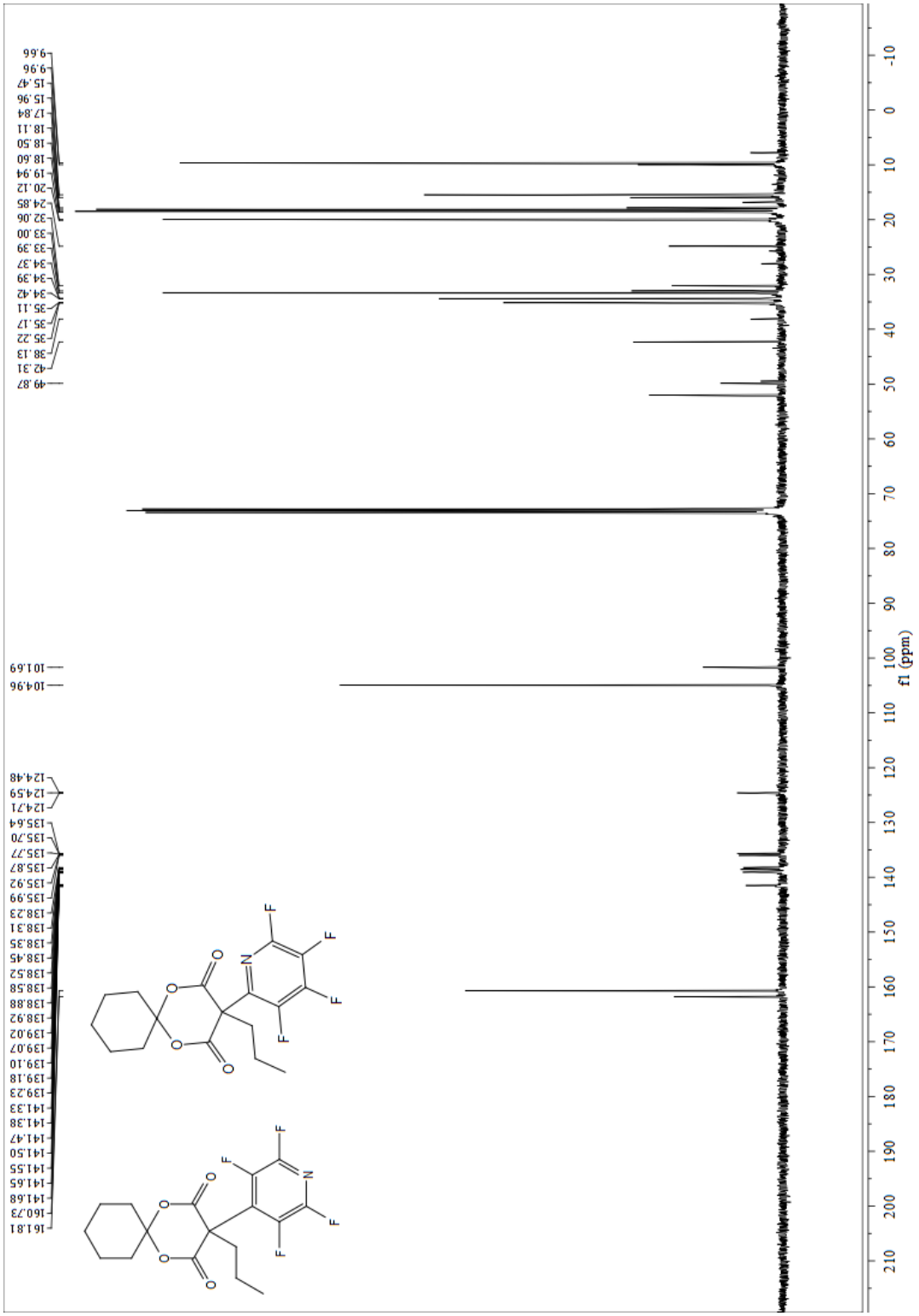
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7b (3-(perfluoropyridin-4-yl)-3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione)



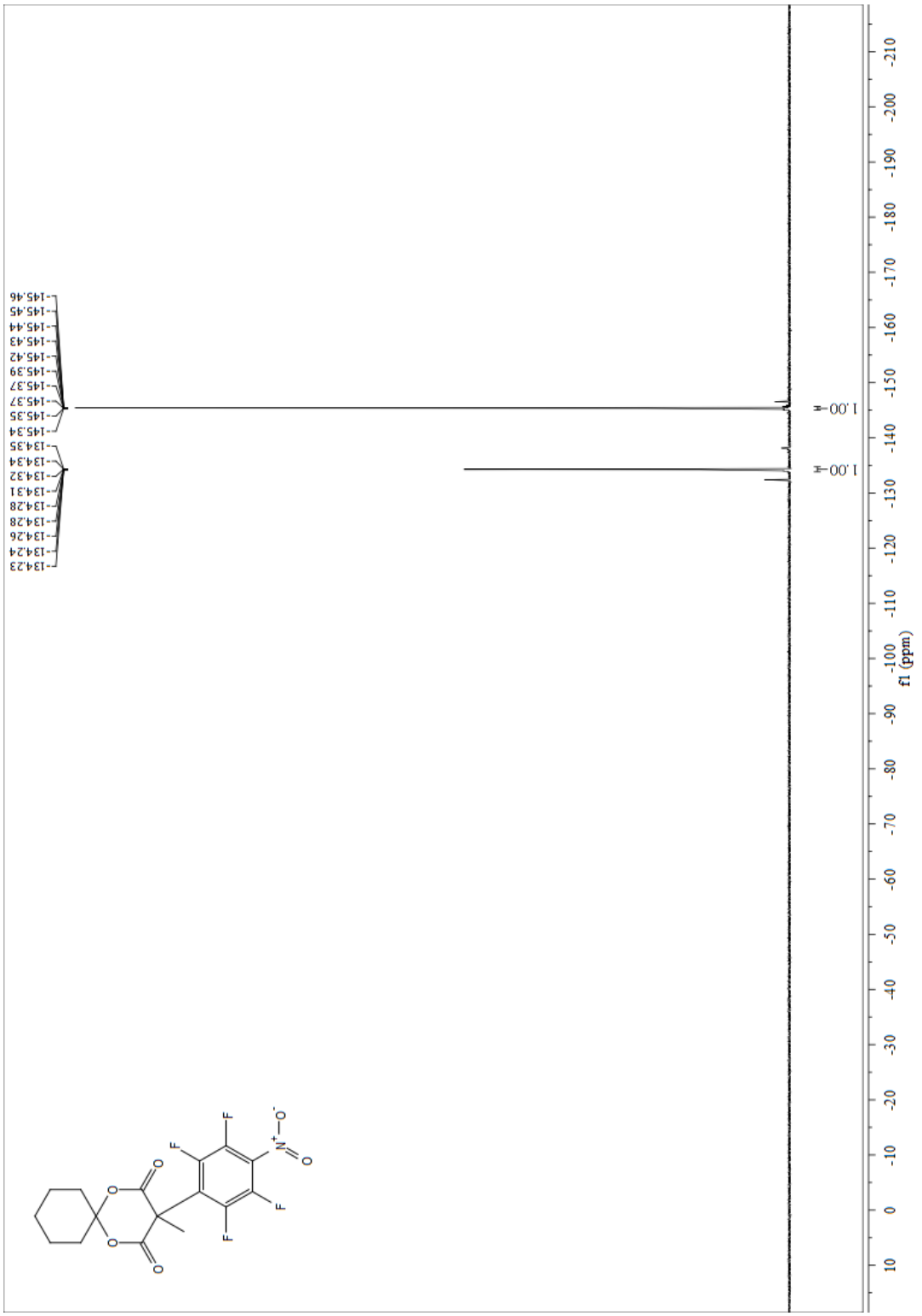
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7b (3-(perfluoropyridin-4-yl)-3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione)



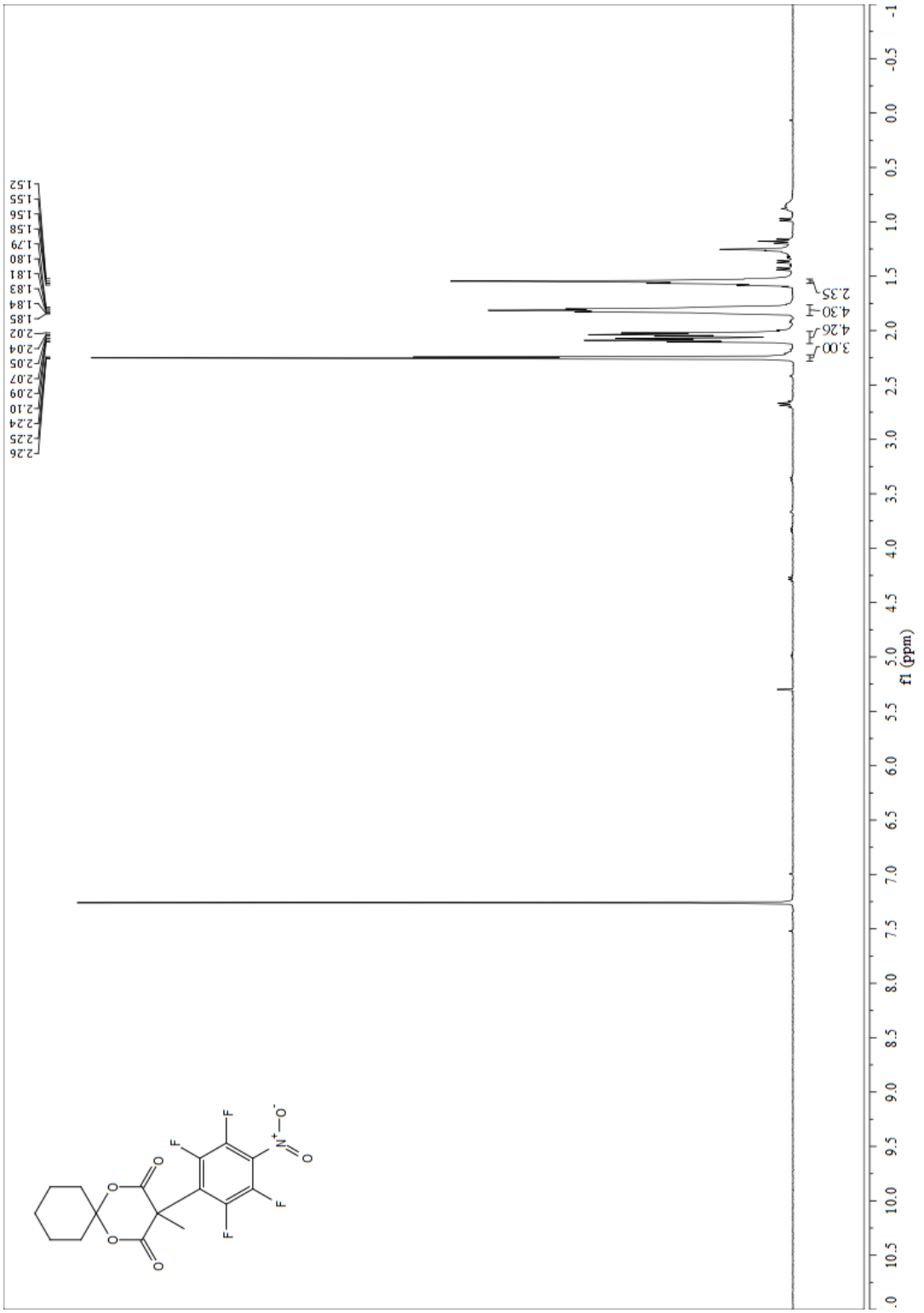
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7b (3-(perfluoropyridin-4-yl)-3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione)



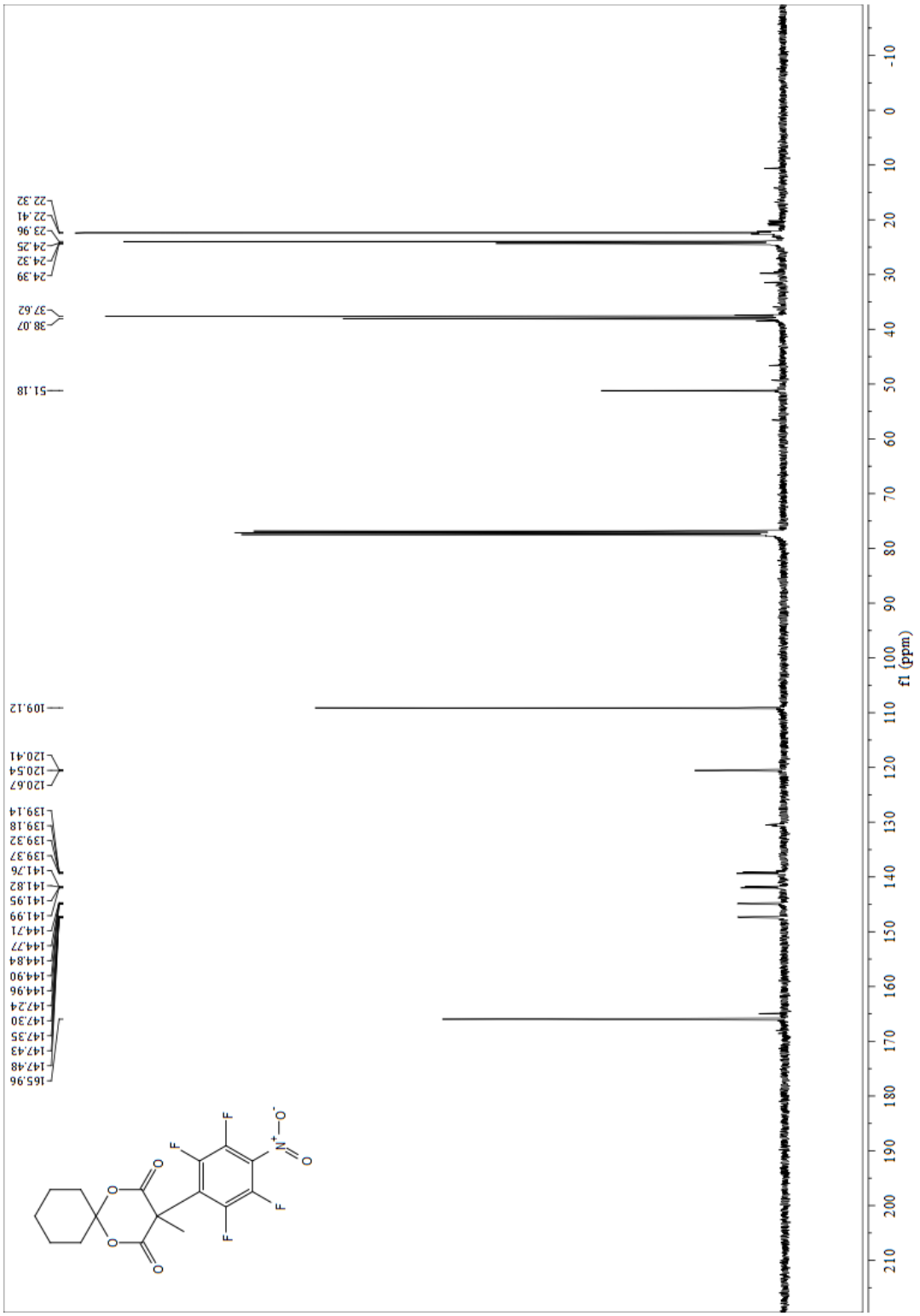
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7c (3-methyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



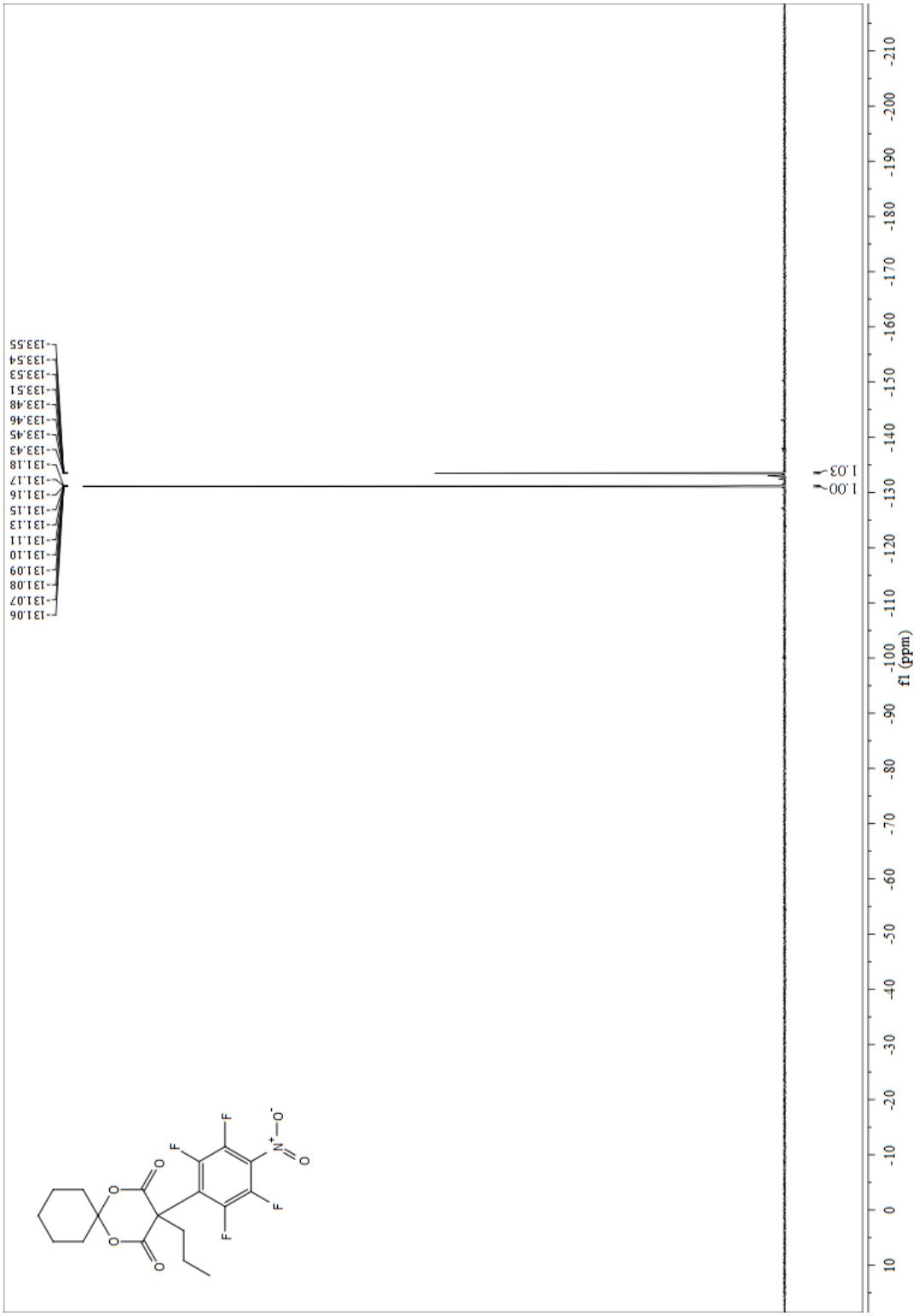
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7c (3-methyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



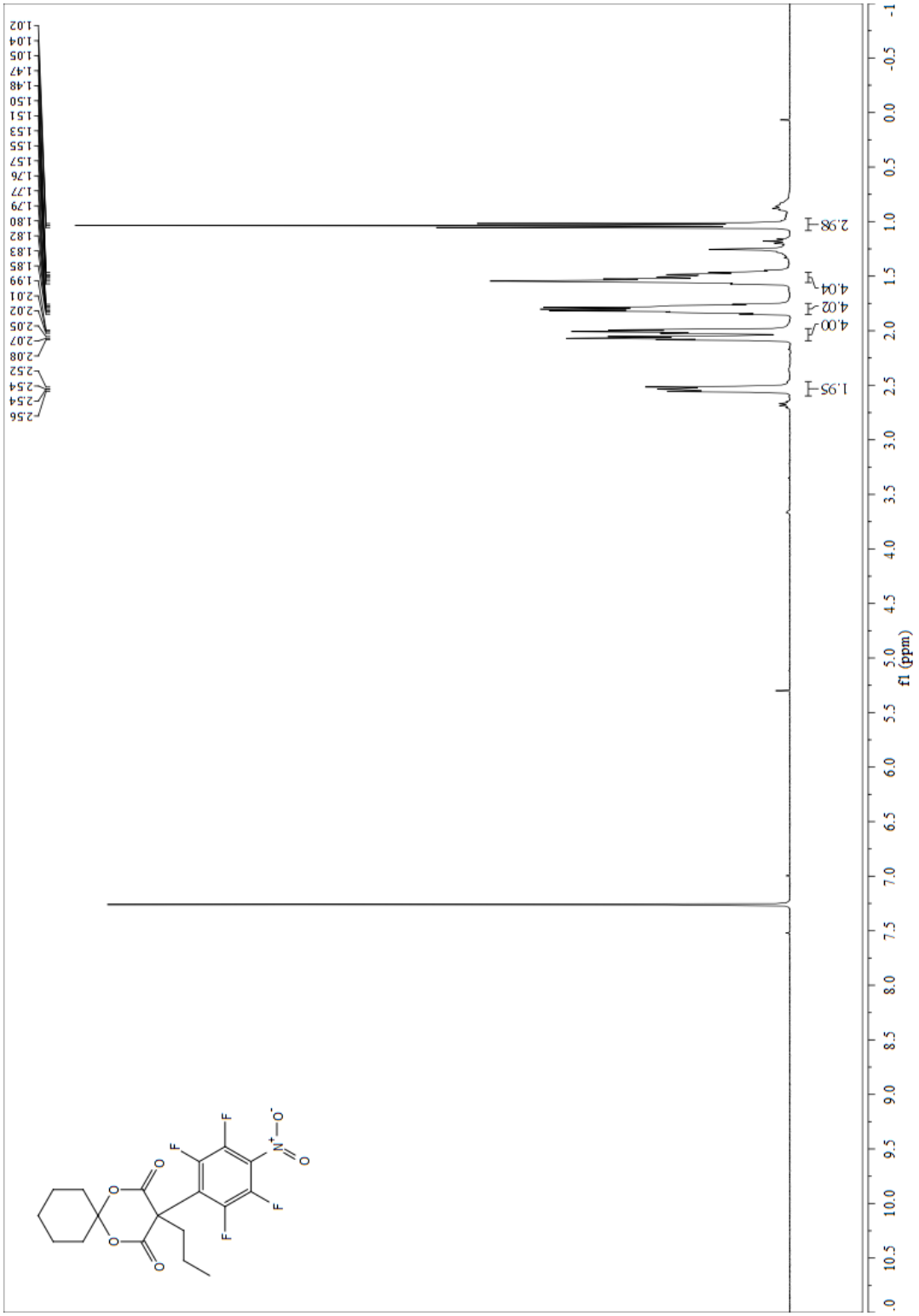
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7c (3-methyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



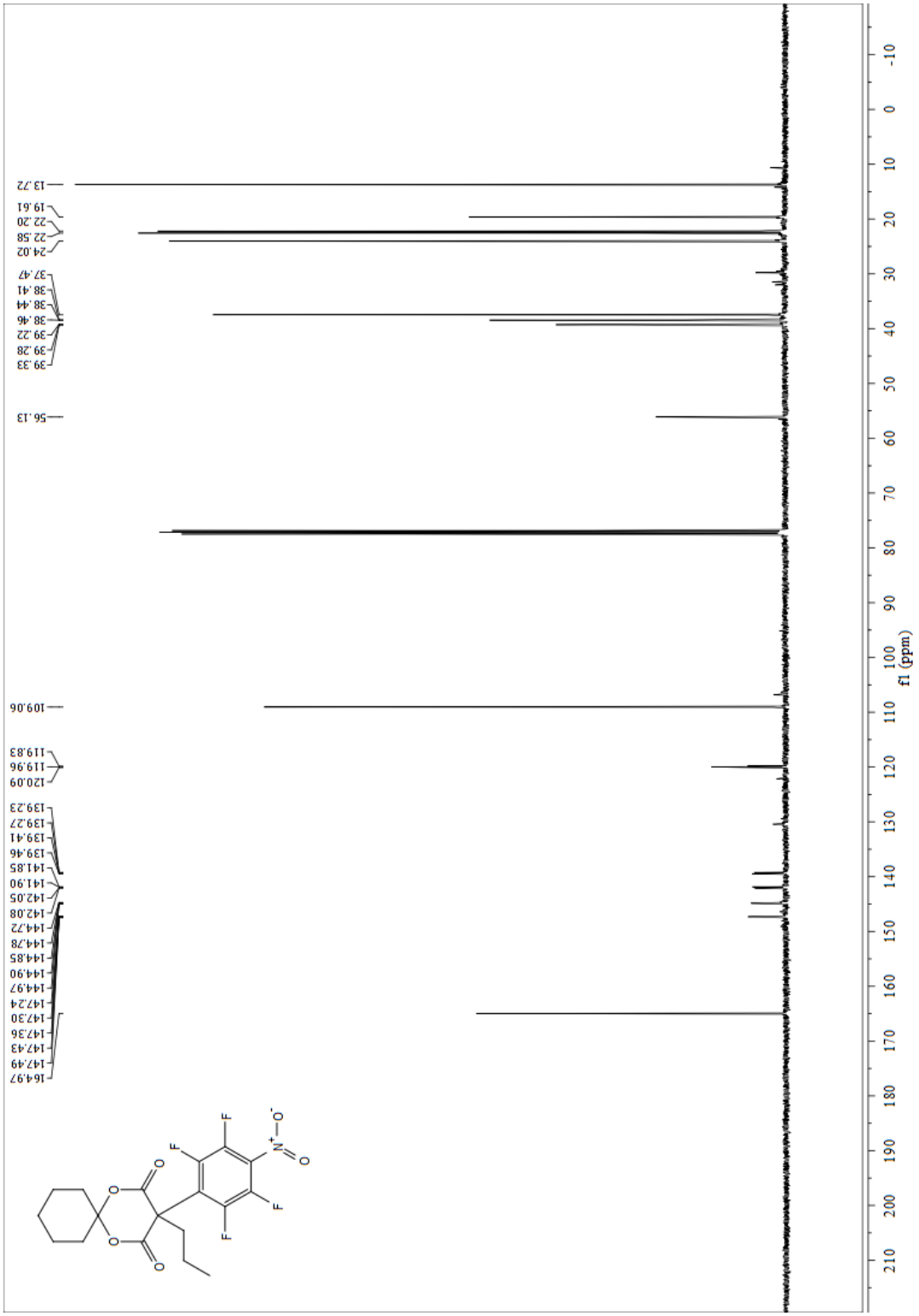
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7d (3-propyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



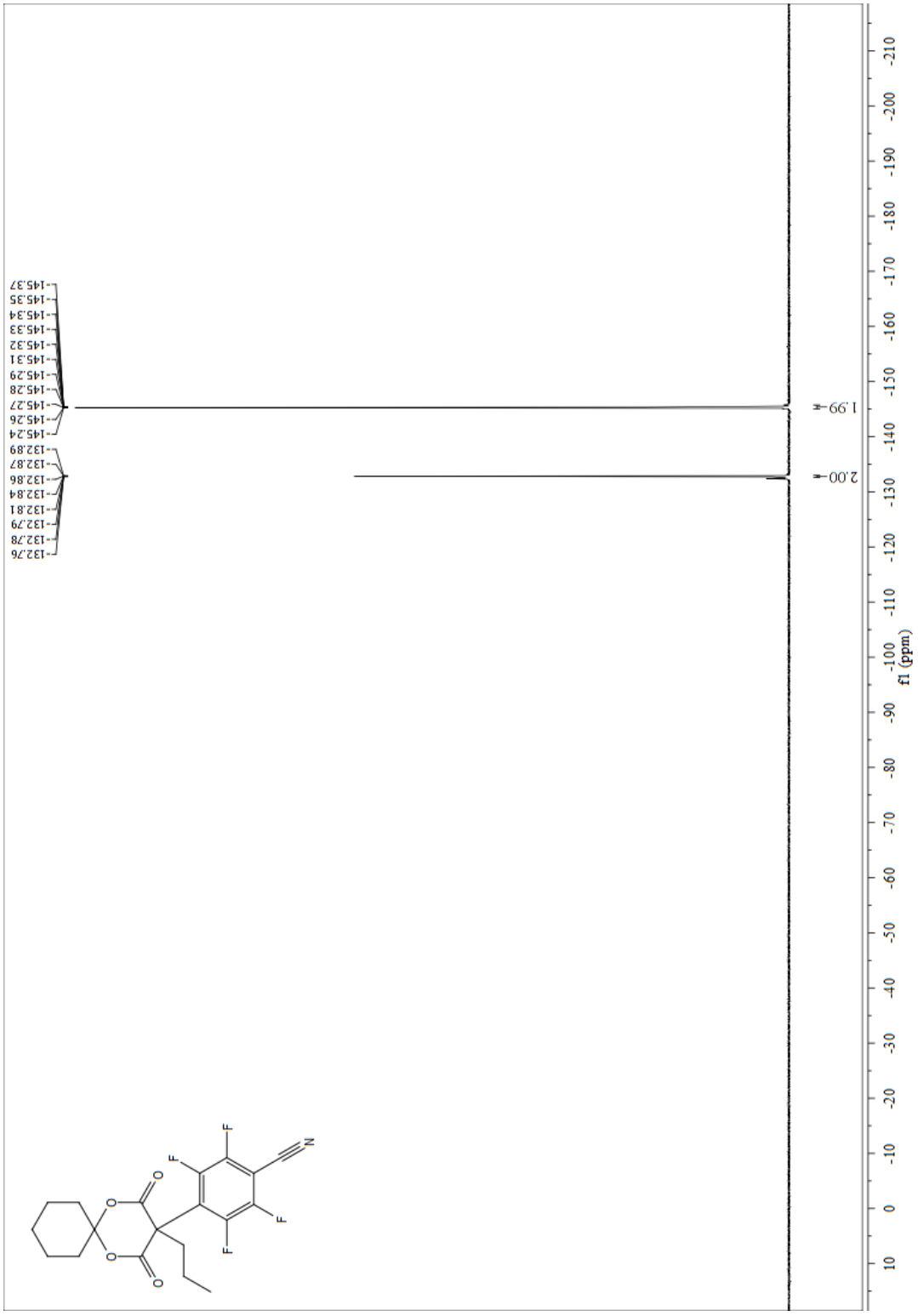
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7d (3-propyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



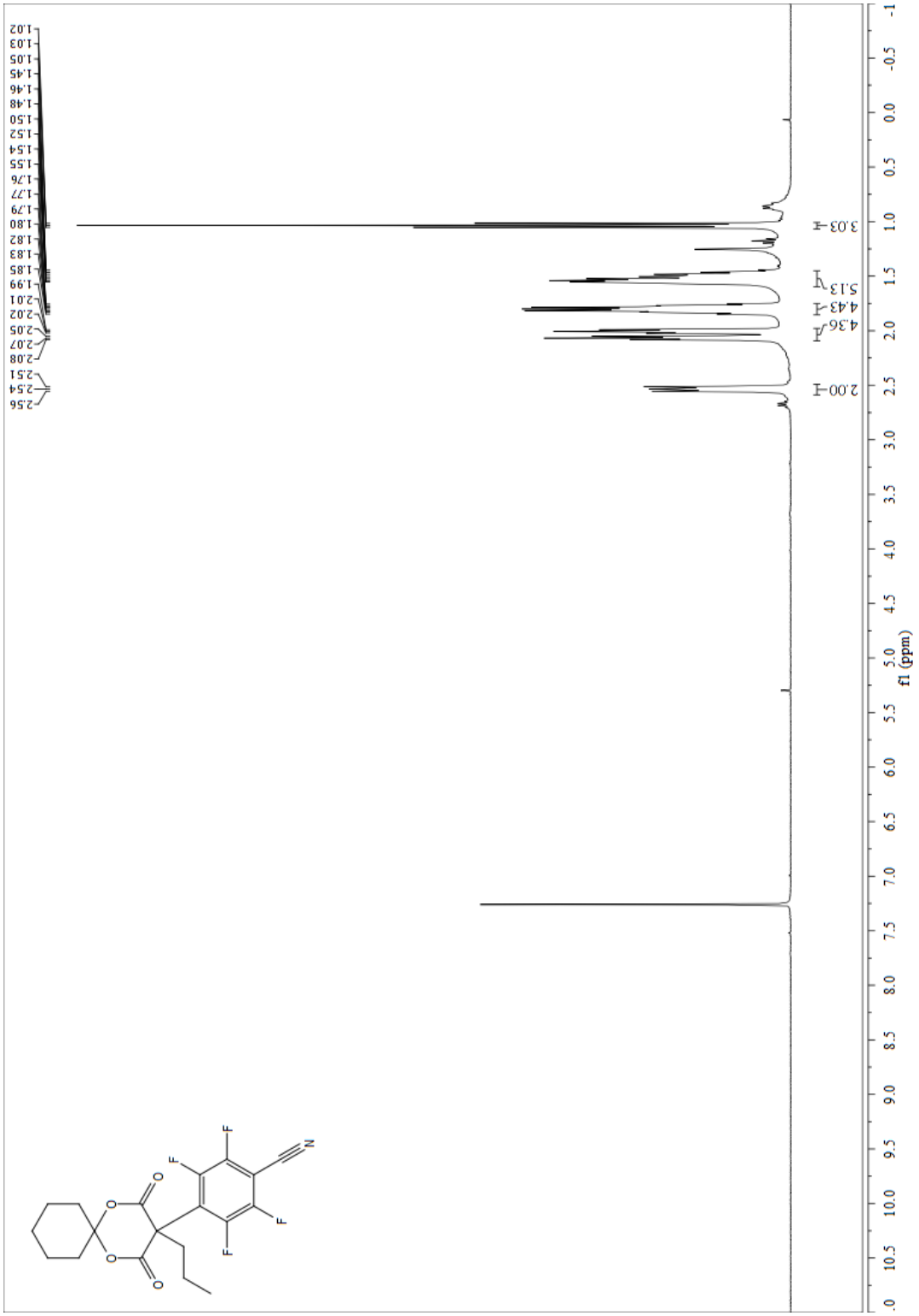
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7d (3-propyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



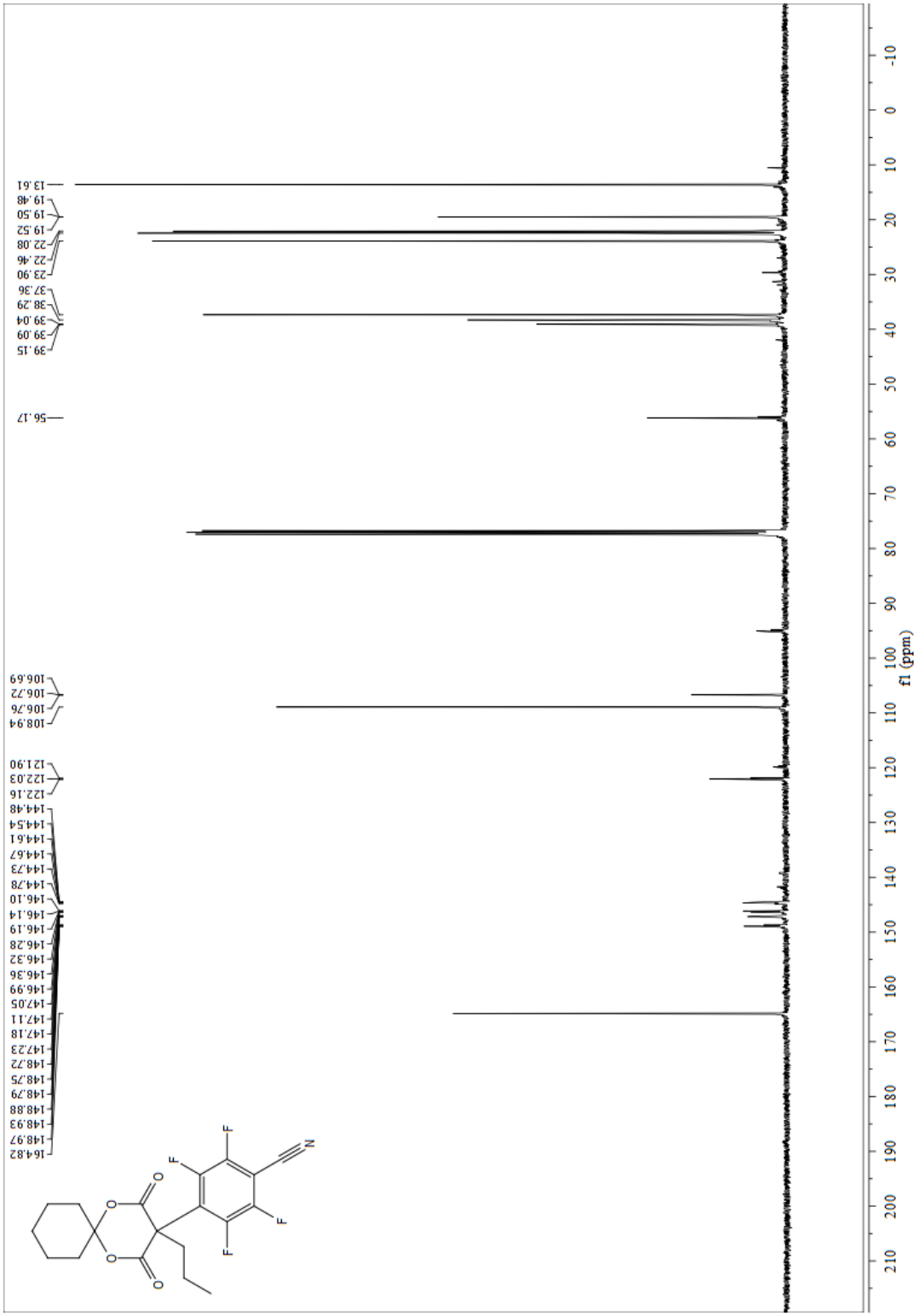
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7e (4-(2,4-dioxo-3-propyl-1,5-dioxaspiro[5.5]undecan-3-yl)-2,3,5,6-tetrafluorobenzonitrile)



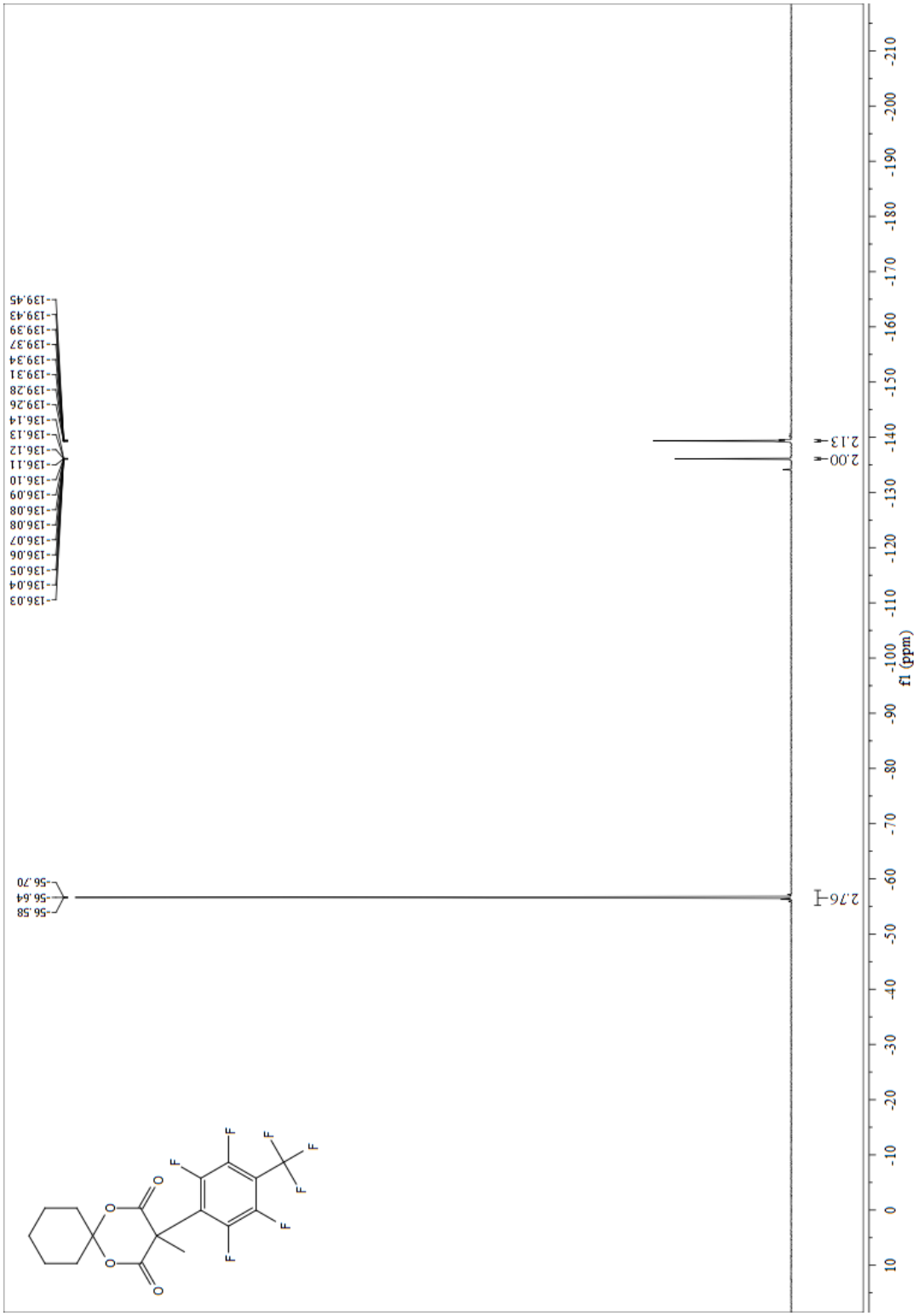
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7e (4-(2,4-dioxo-3-propyl-1,5-dioxaspiro[5.5]undecan-3-yl)-2,3,5,6-tetrafluorobenzonitrile)



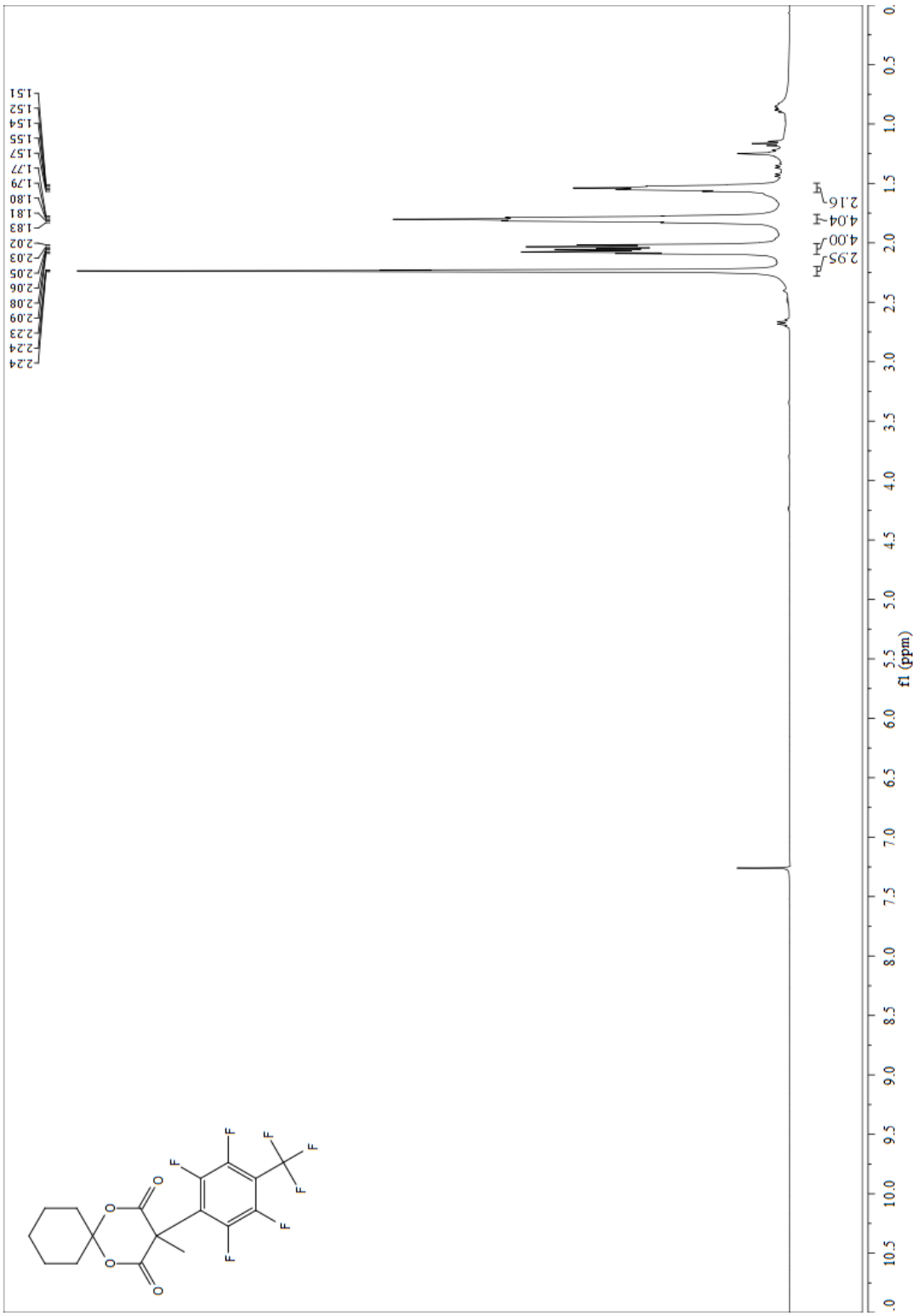
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7e (4-(2,4-dioxo-3-propyl-1,5-dioxaspiro[5.5]undecan-3-yl)-2,3,5,6-tetrafluorobenzonitrile)



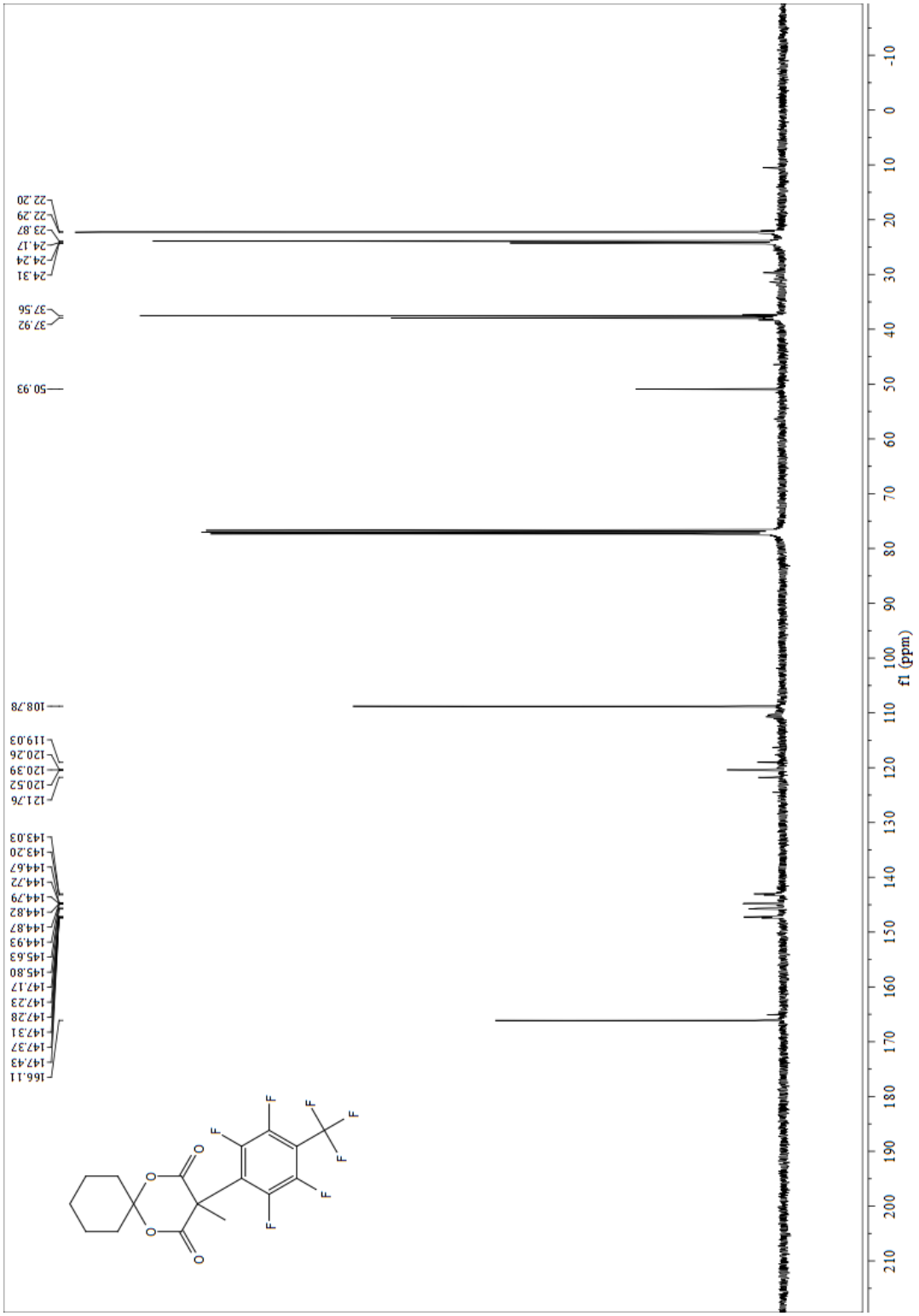
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7f (3-methyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



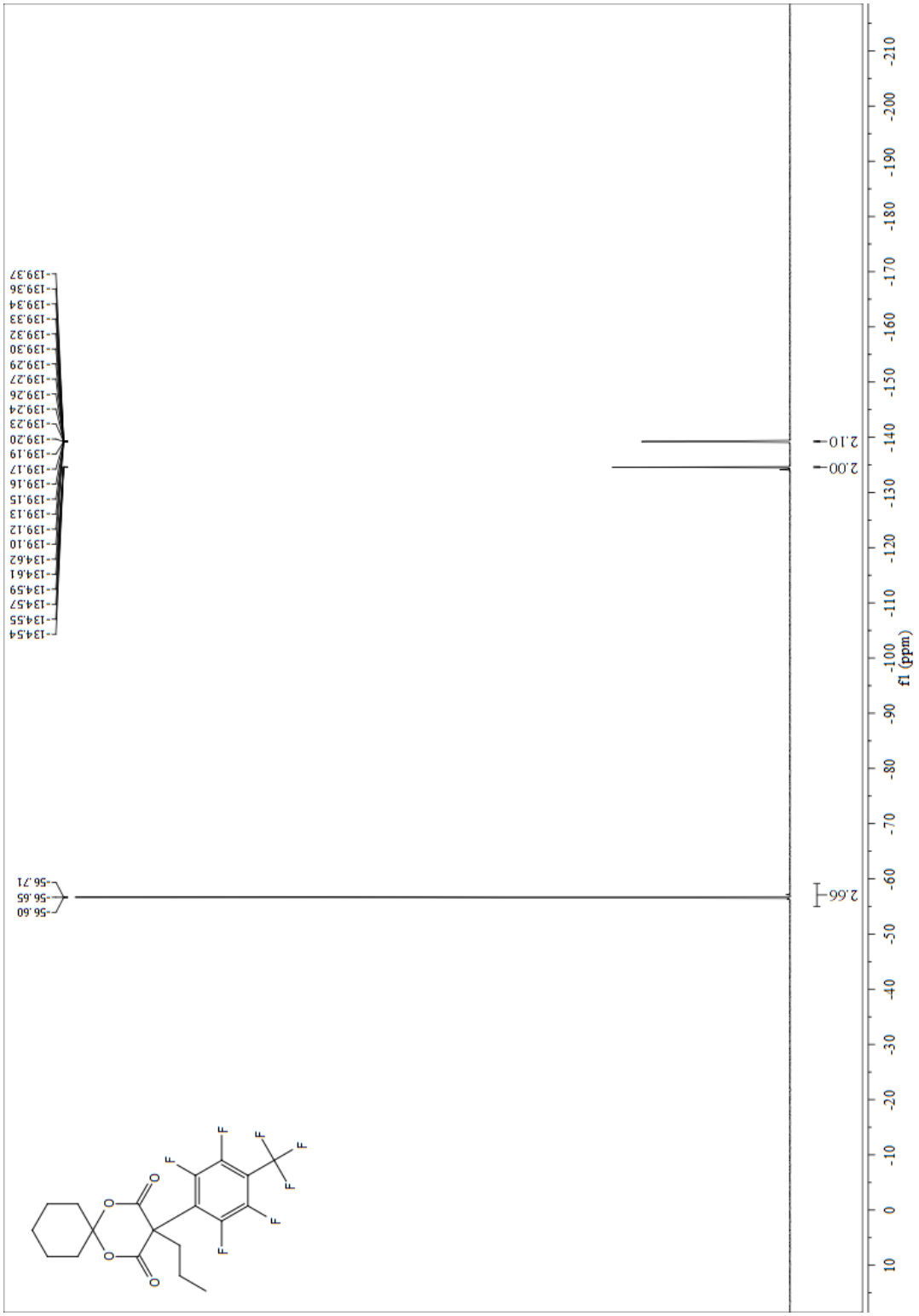
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7f (3-methyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



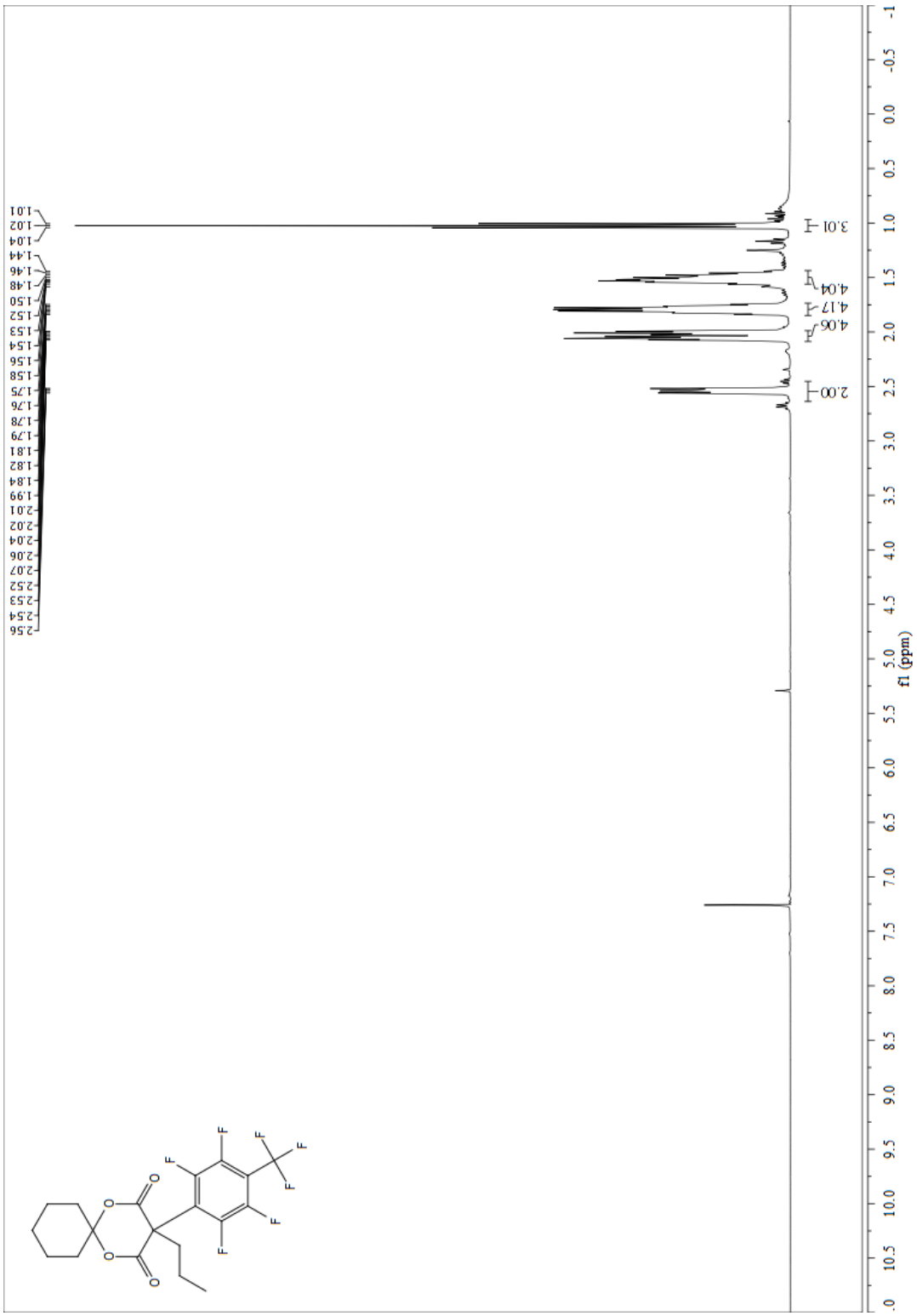
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7f (3-methyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



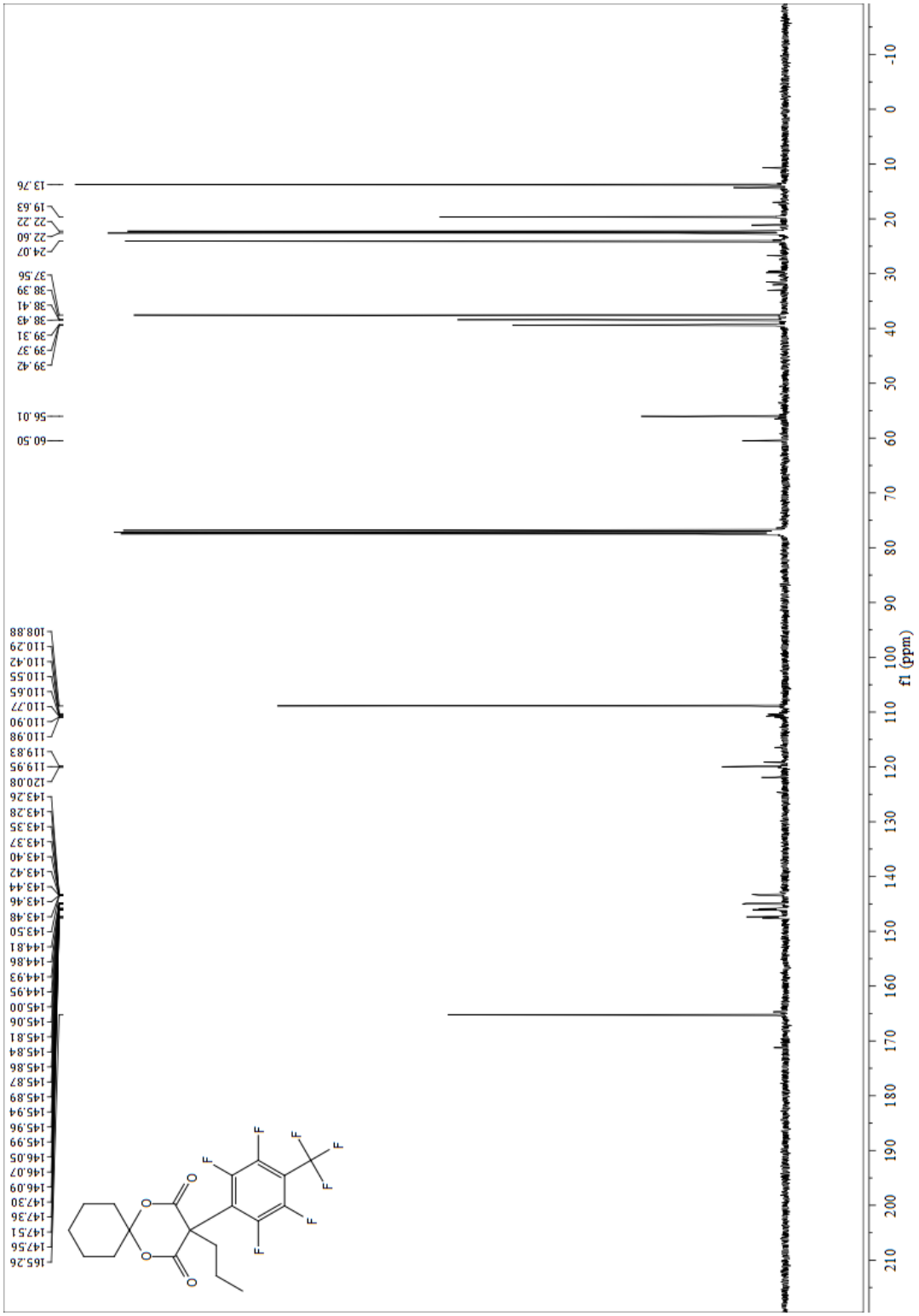
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7g (3-propyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



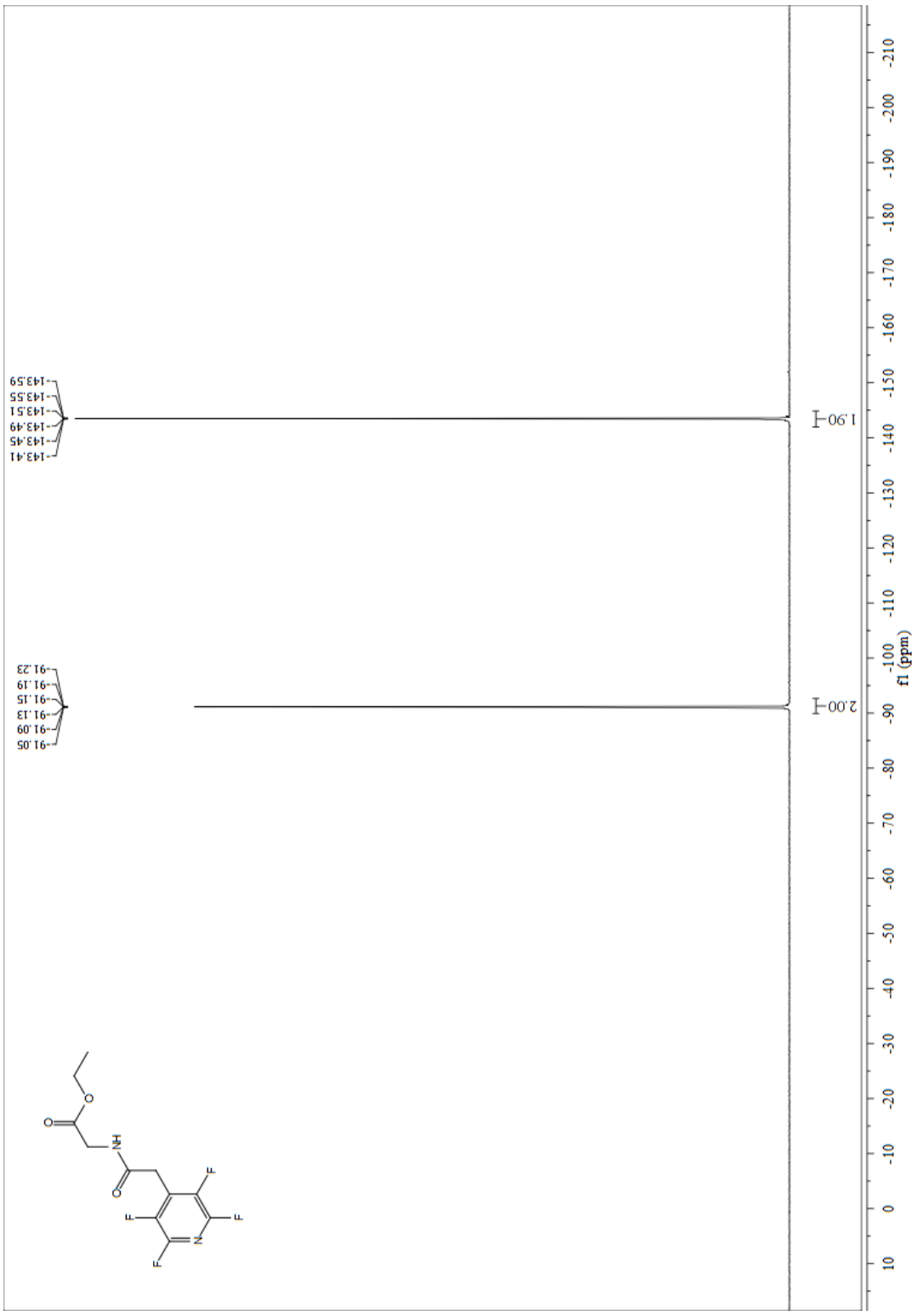
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7g (3-propyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



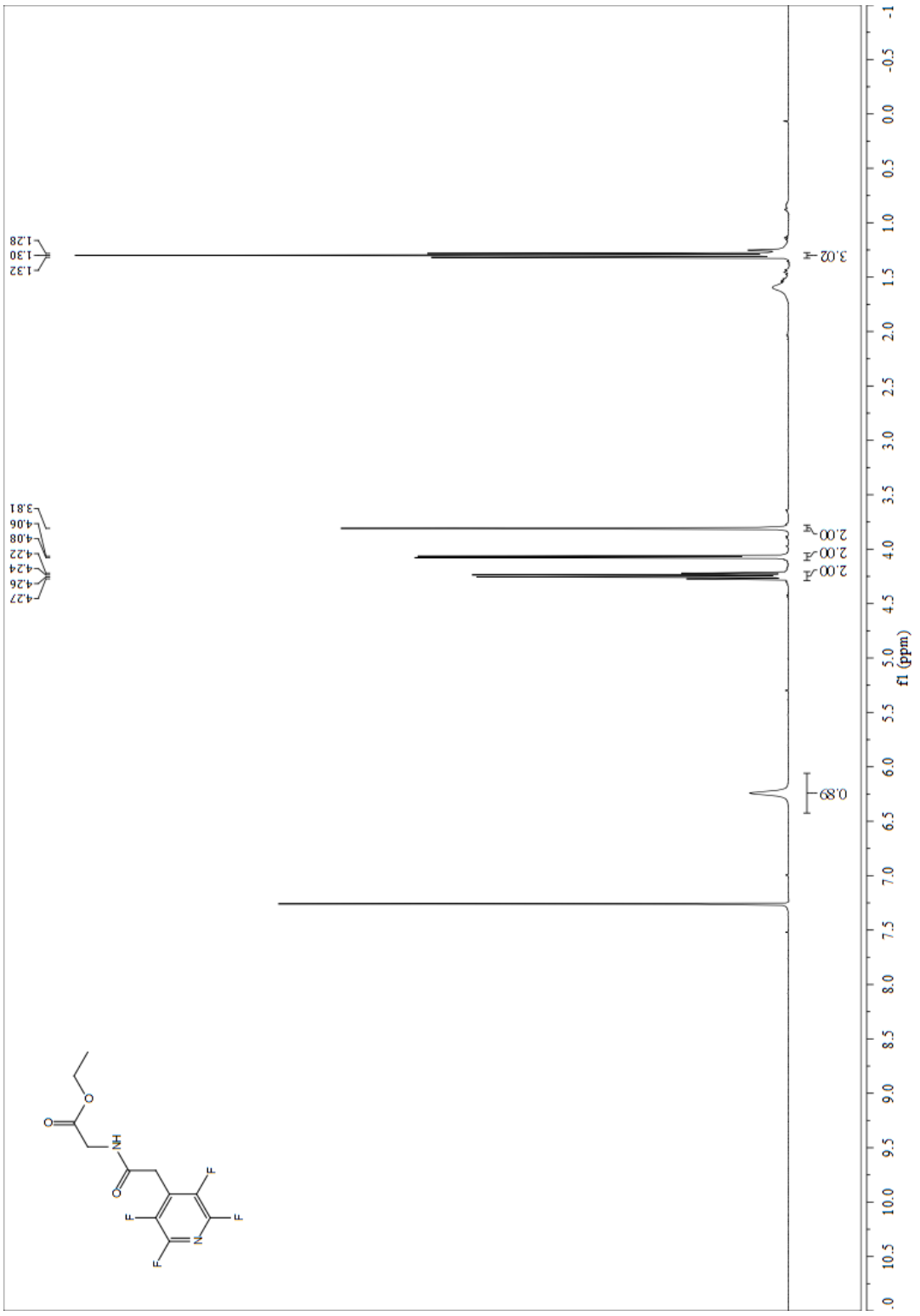
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.7g (3-propyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione)



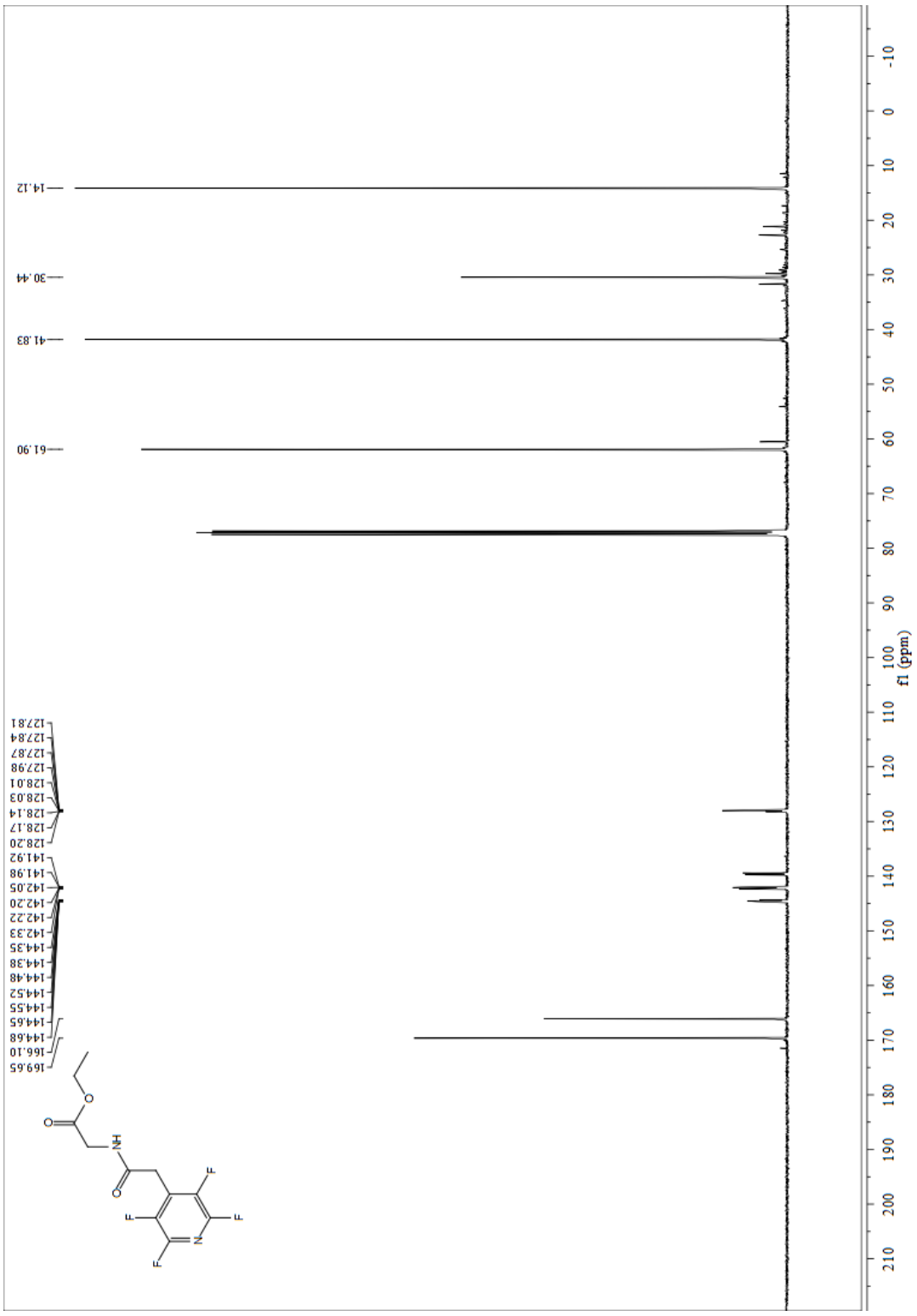
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8a (Ethyl 2-(2-(perfluoropyridin-4-yl)acetamido)acetate)



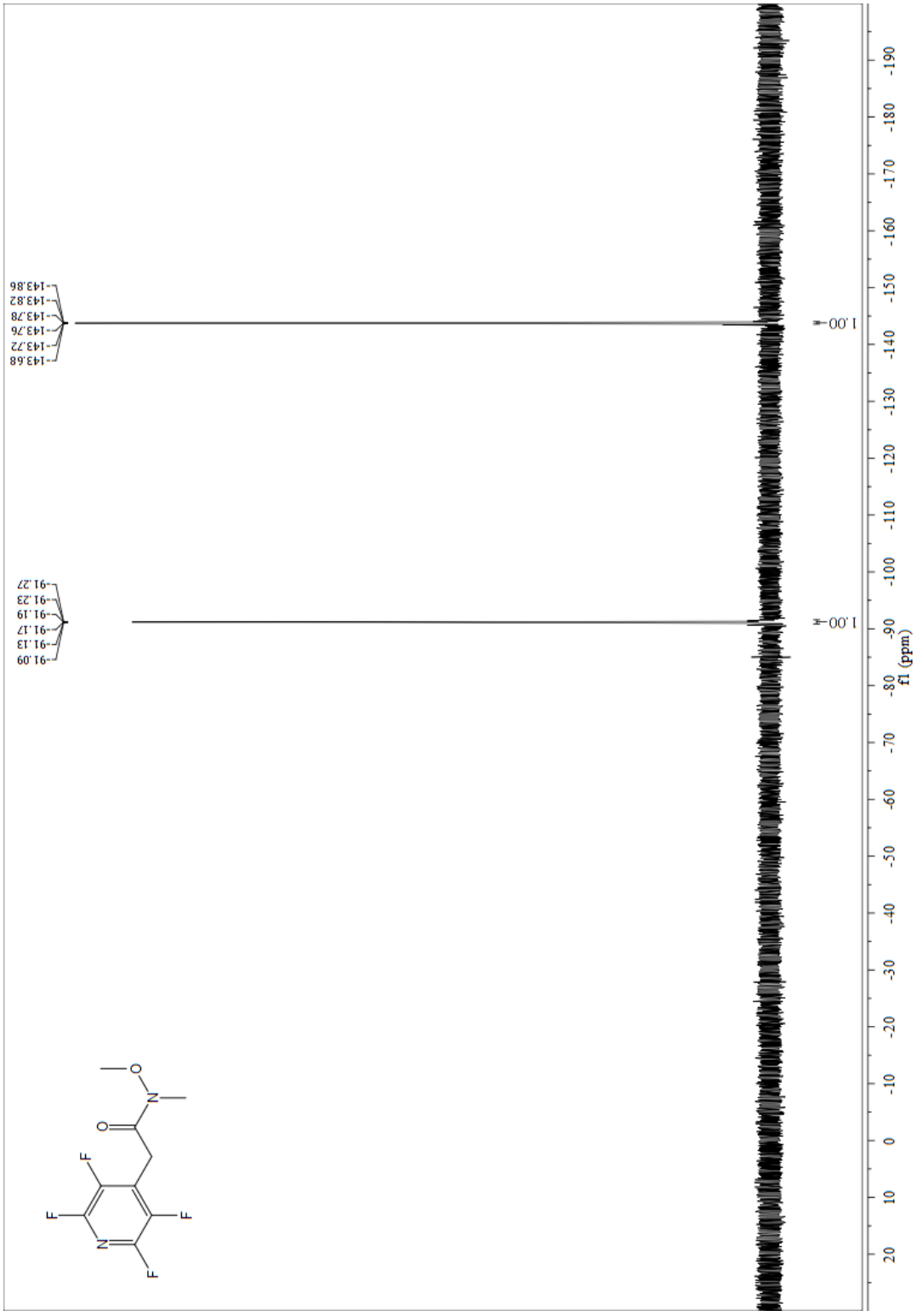
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8a (Ethyl 2-(2-(perfluoropyridin-4-yl)acetamido)acetate)



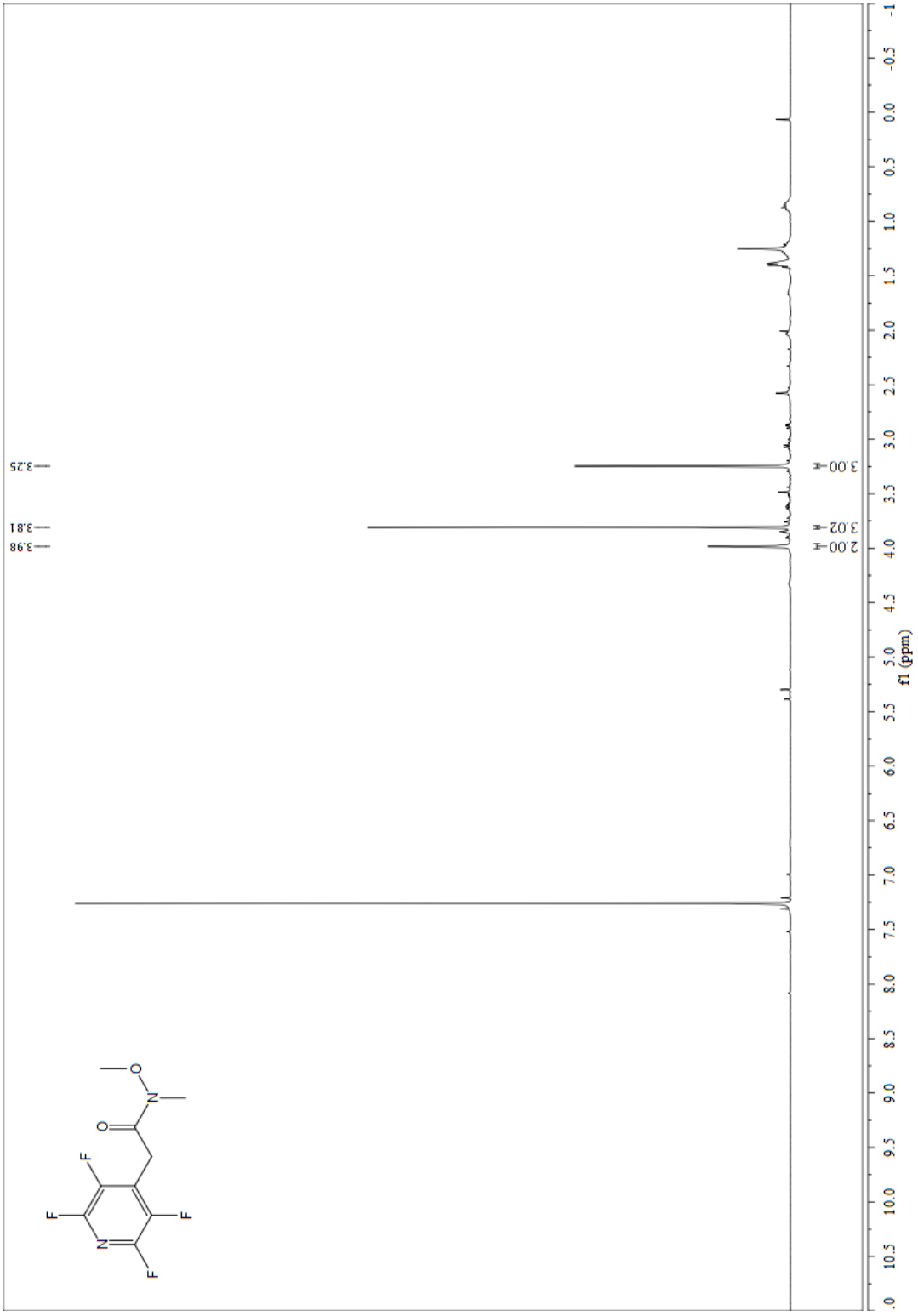
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8a (Ethyl 2-(2-(perfluoropyridin-4-yl)acetamido)acetate)



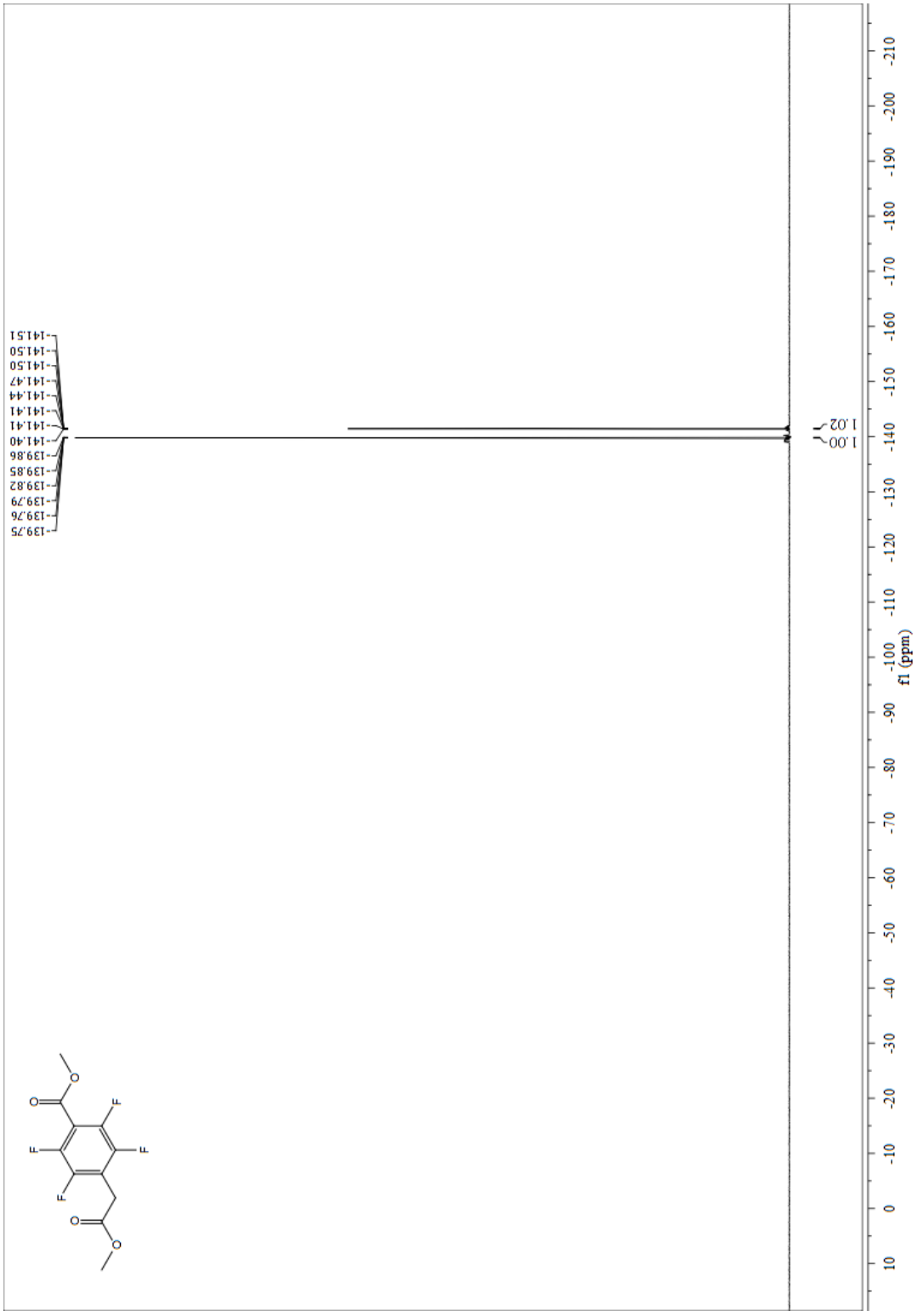
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8b (*N*-methoxy-*N*-methyl-2-(perfluoropyridin-4-yl)acetamide)



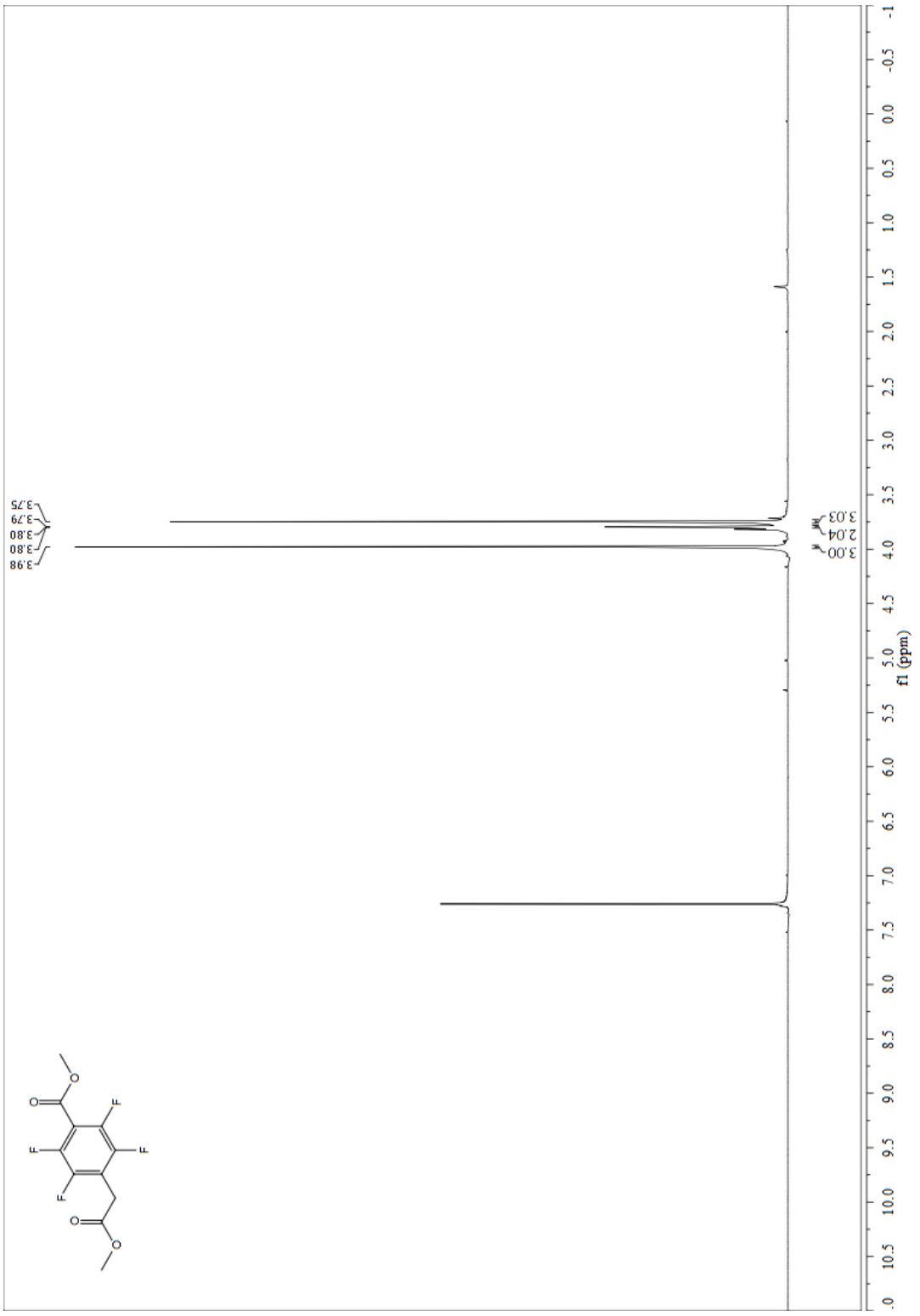
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8b (*N*-methoxy-*N*-methyl-2-(perfluoropyridin-4-yl)acetamide)



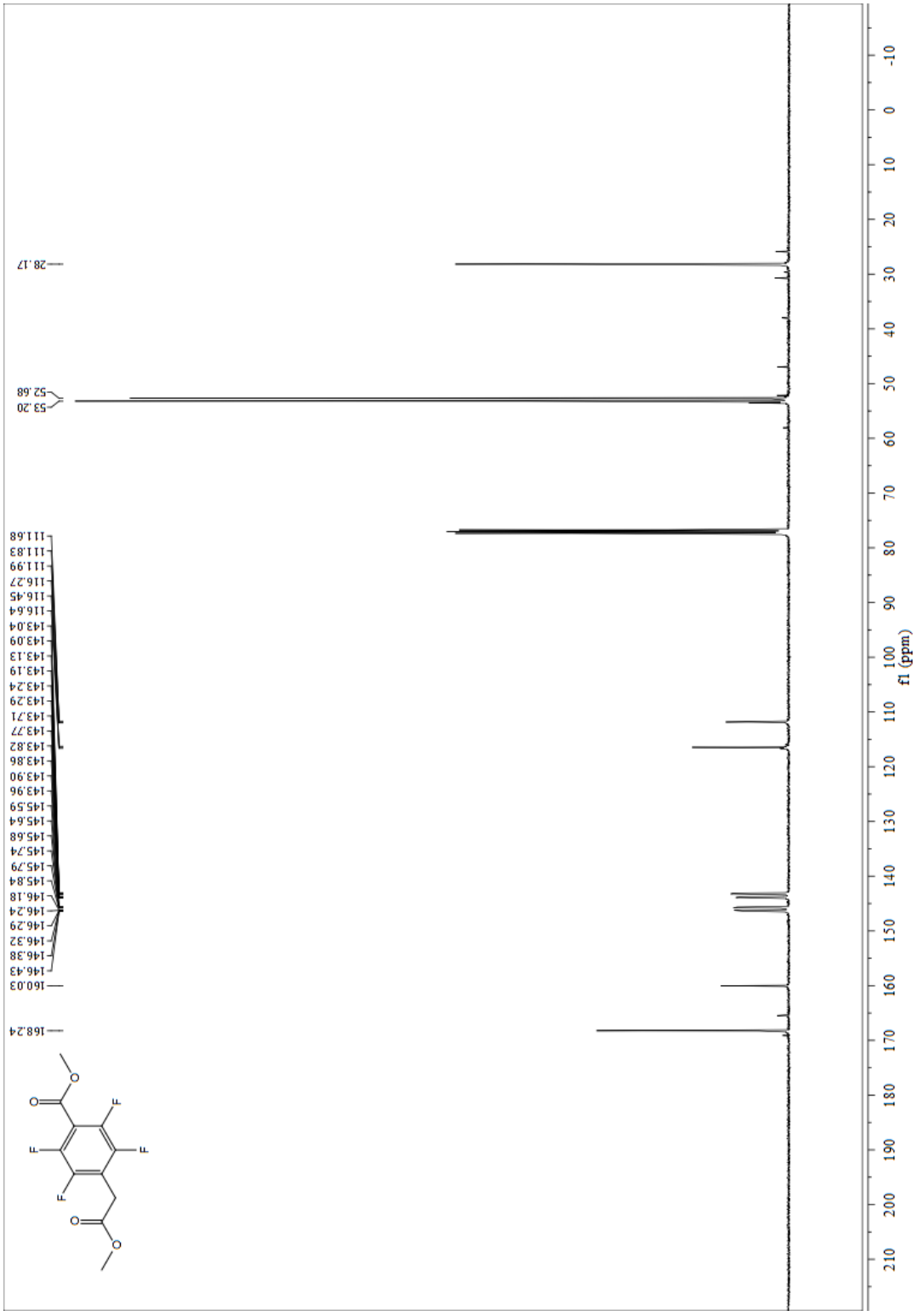
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8c (Methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate)



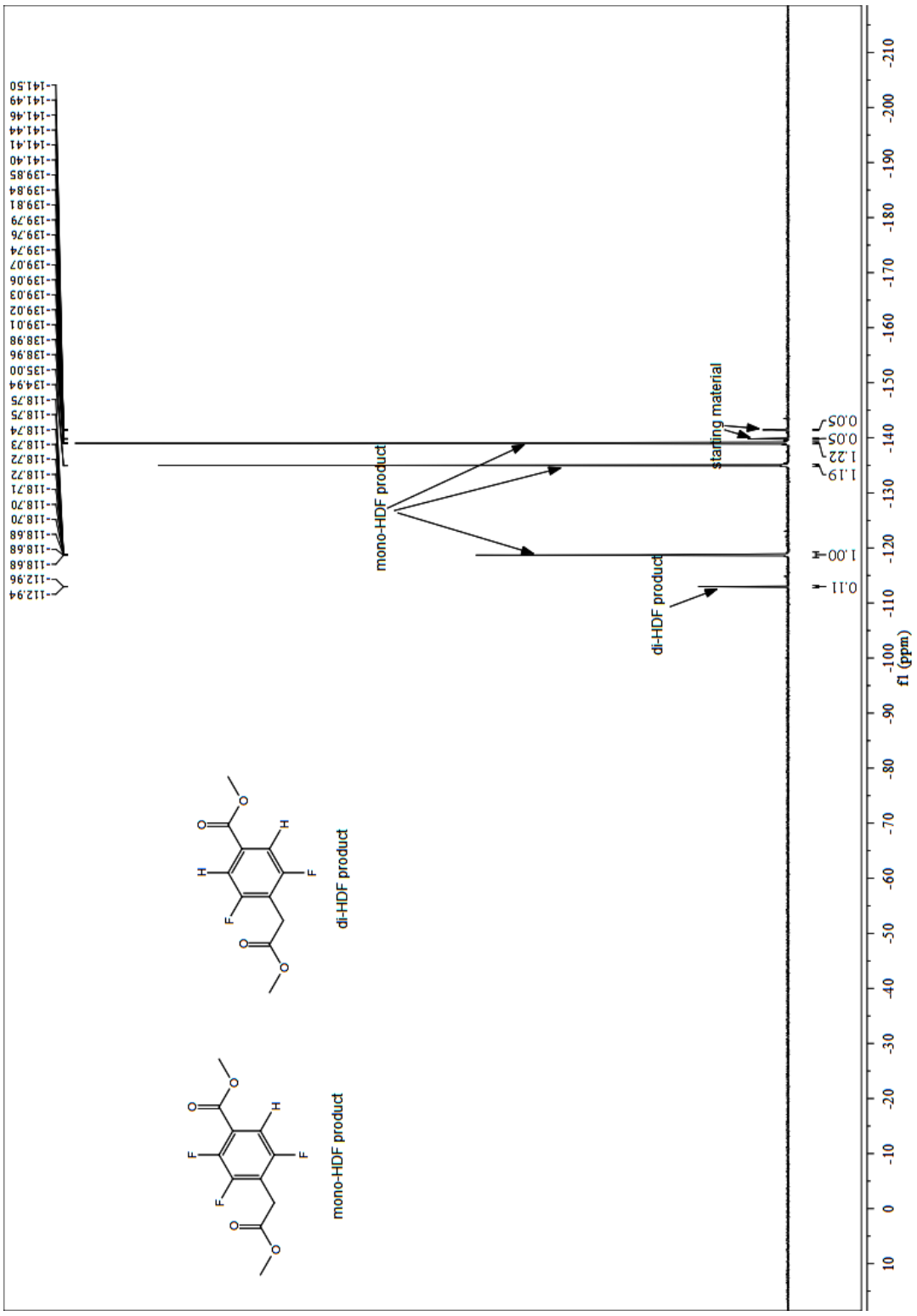
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8c (Methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate)



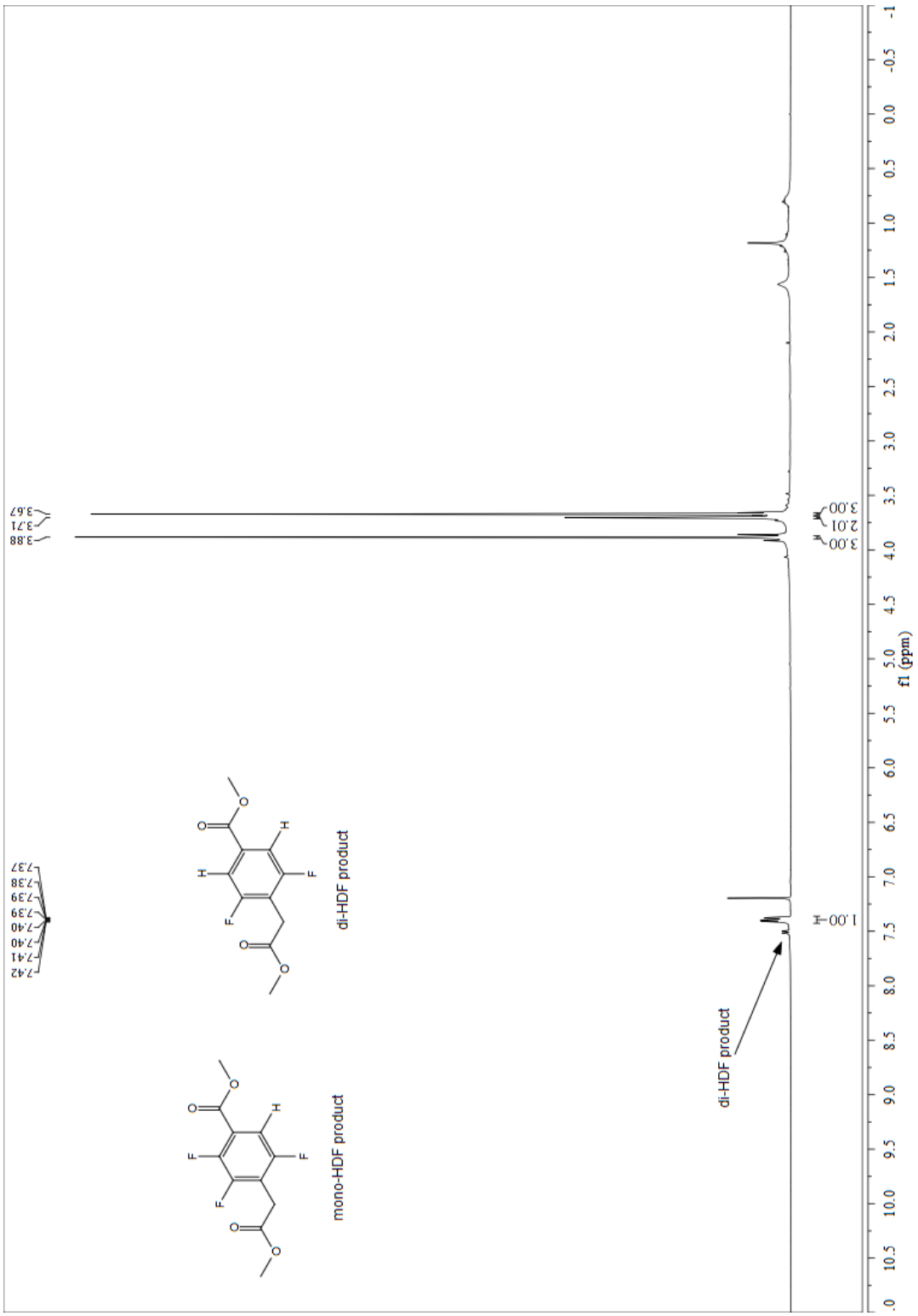
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8c (Methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate)



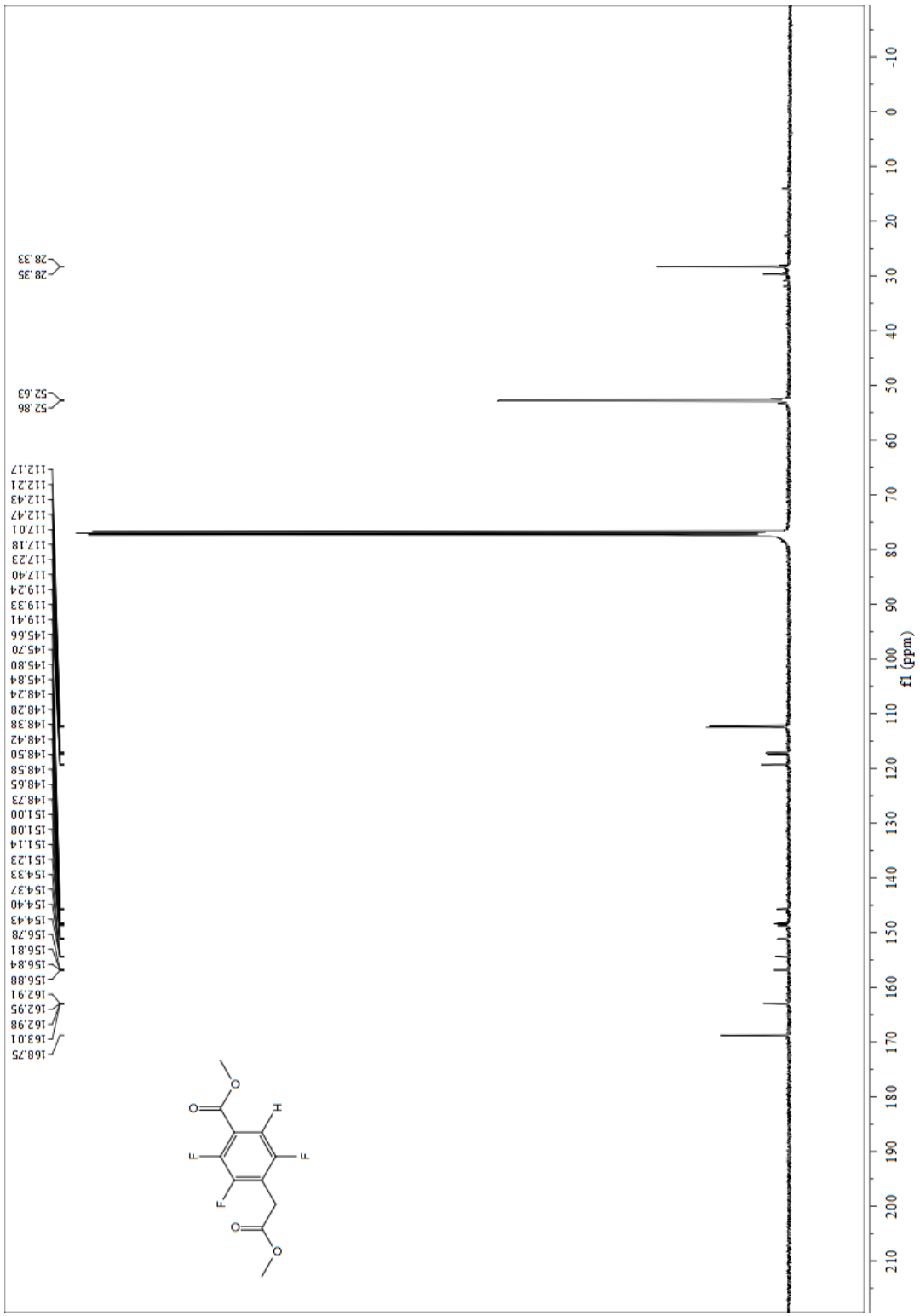
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8d (Methyl 2,3,5-trifluoro-4-(2-methoxy-2-oxoethyl)benzoate)



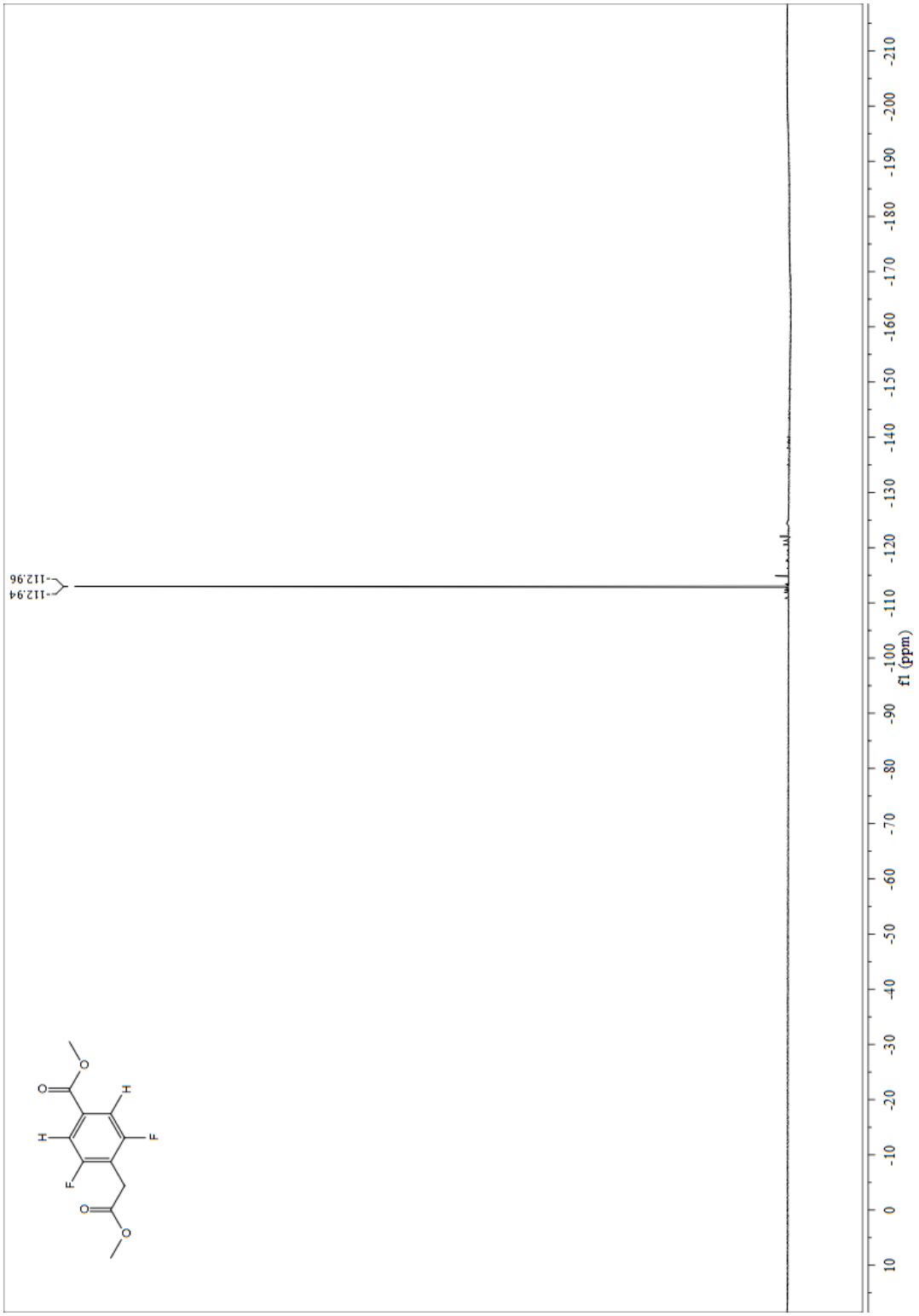
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8d (Methyl 2,3,5-trifluoro-4-(2-methoxy-2-oxoethyl)benzoate)



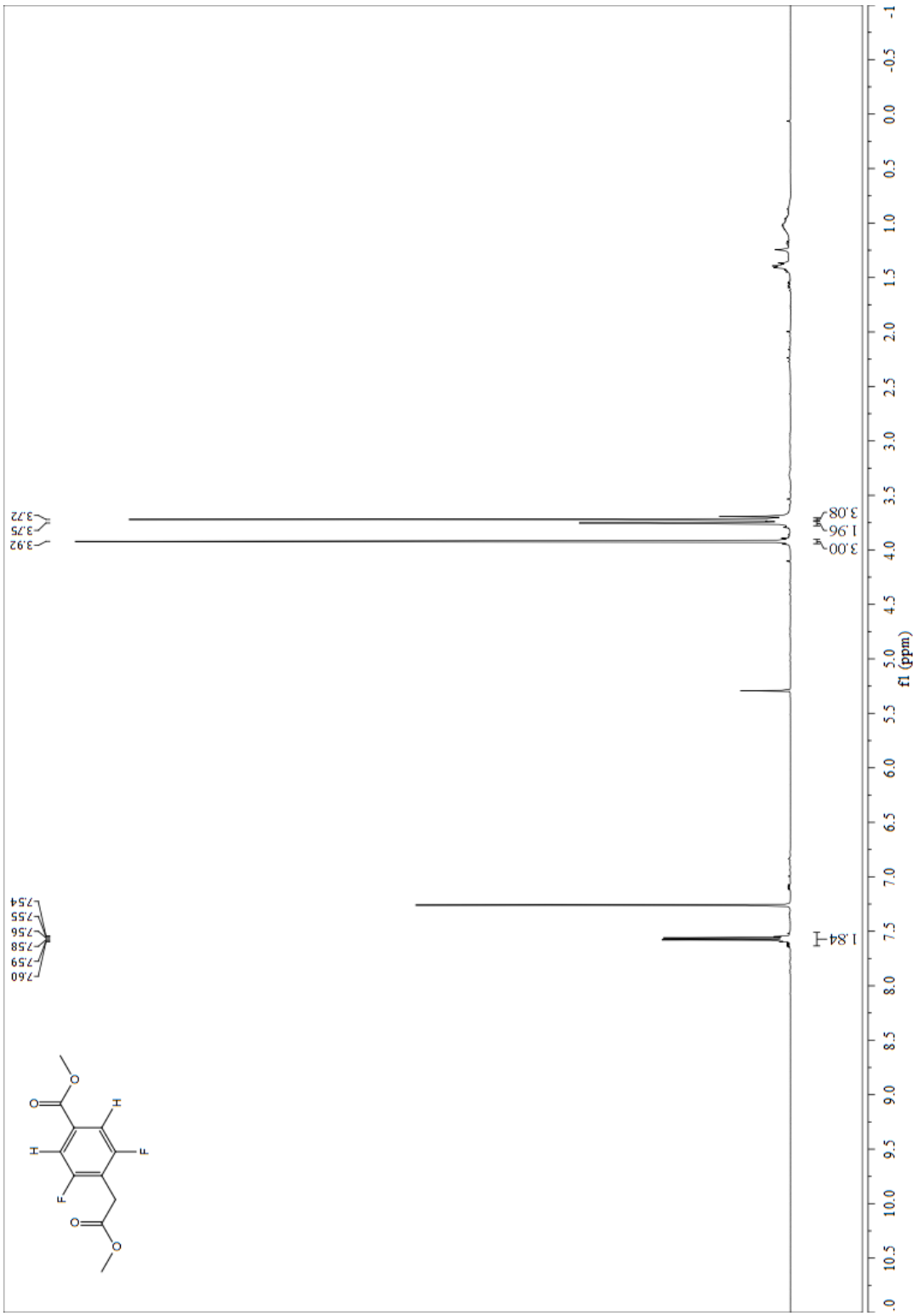
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8d (Methyl 2,3,5-trifluoro-4-(2-methoxy-2-oxoethyl)benzoate)



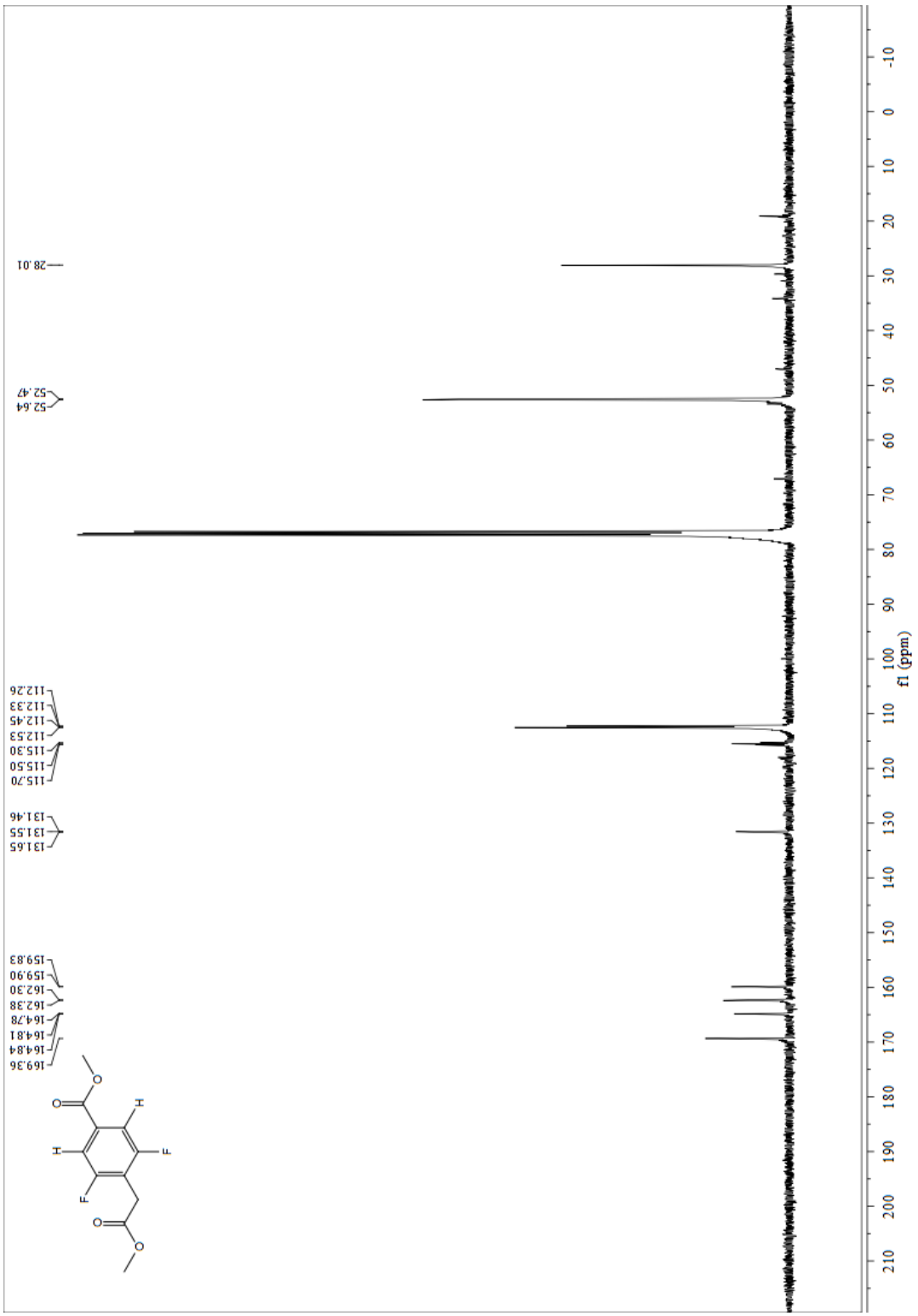
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8e (Methyl 3,5-difluoro-4-(2-methoxy-2-oxoethyl)benzoate)



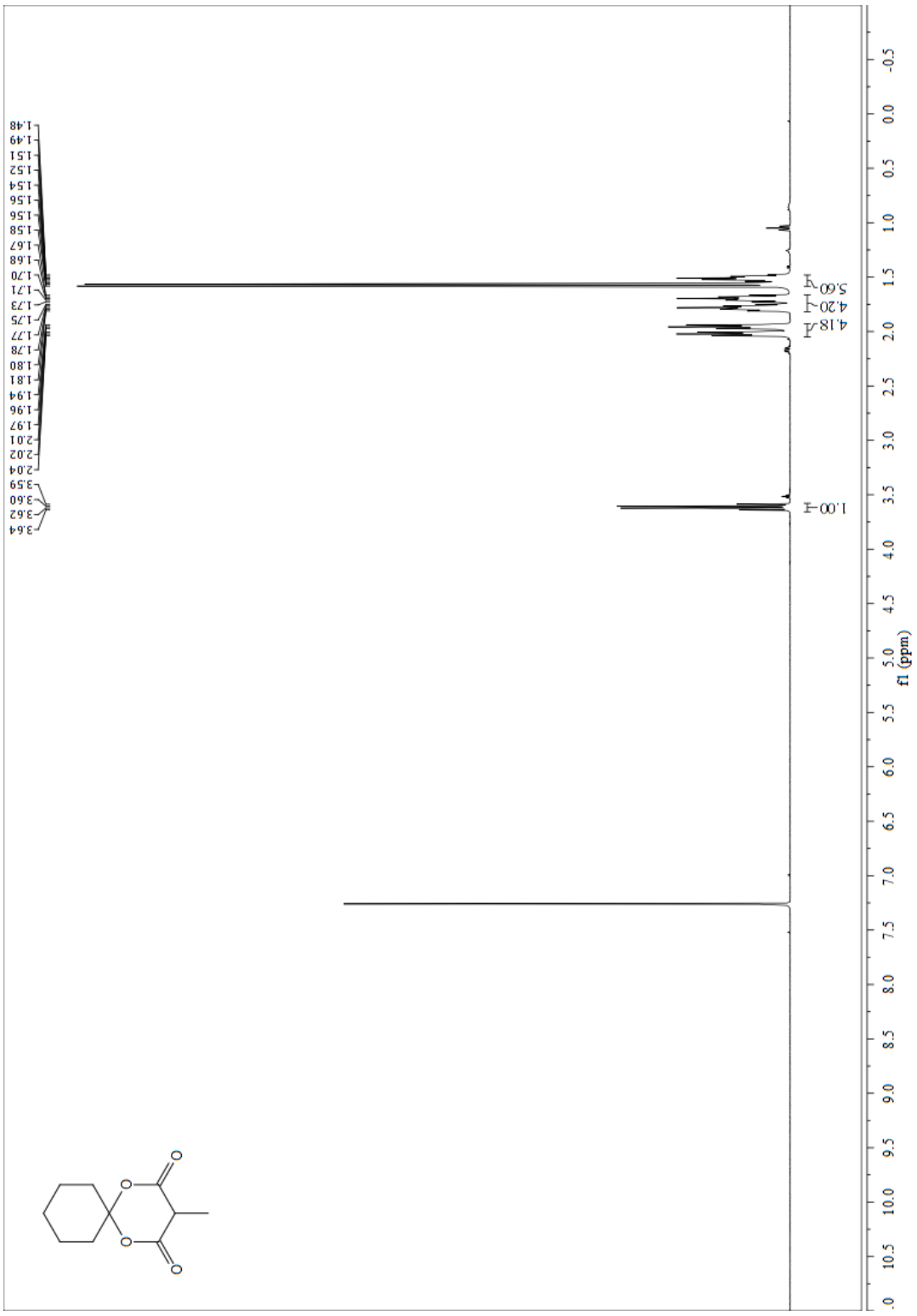
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8e (Methyl 3,5-difluoro-4-(2-methoxy-2-oxoethyl)benzoate)



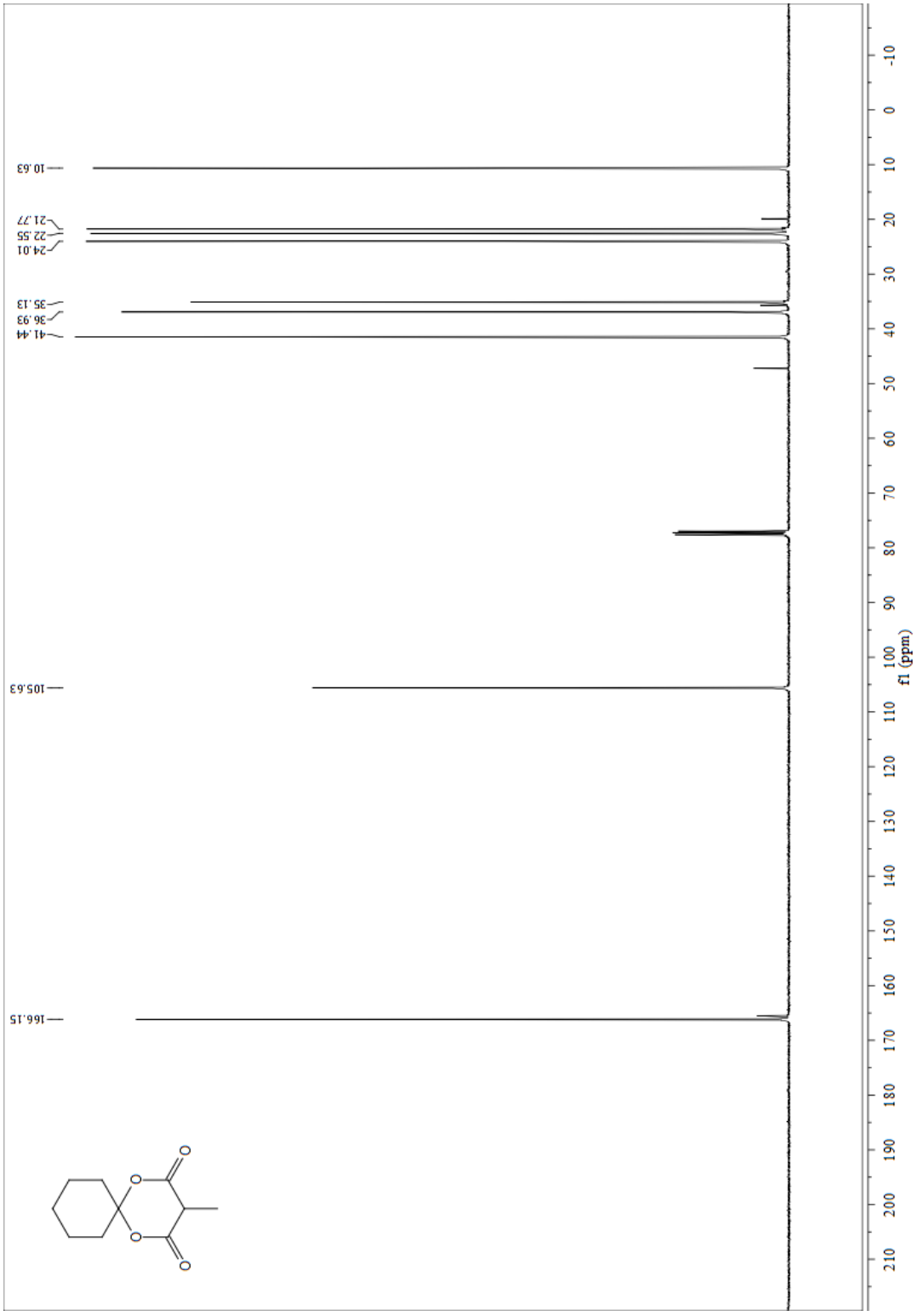
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4.8e (Methyl 3,5-difluoro-4-(2-methoxy-2-oxoethyl)benzoate)



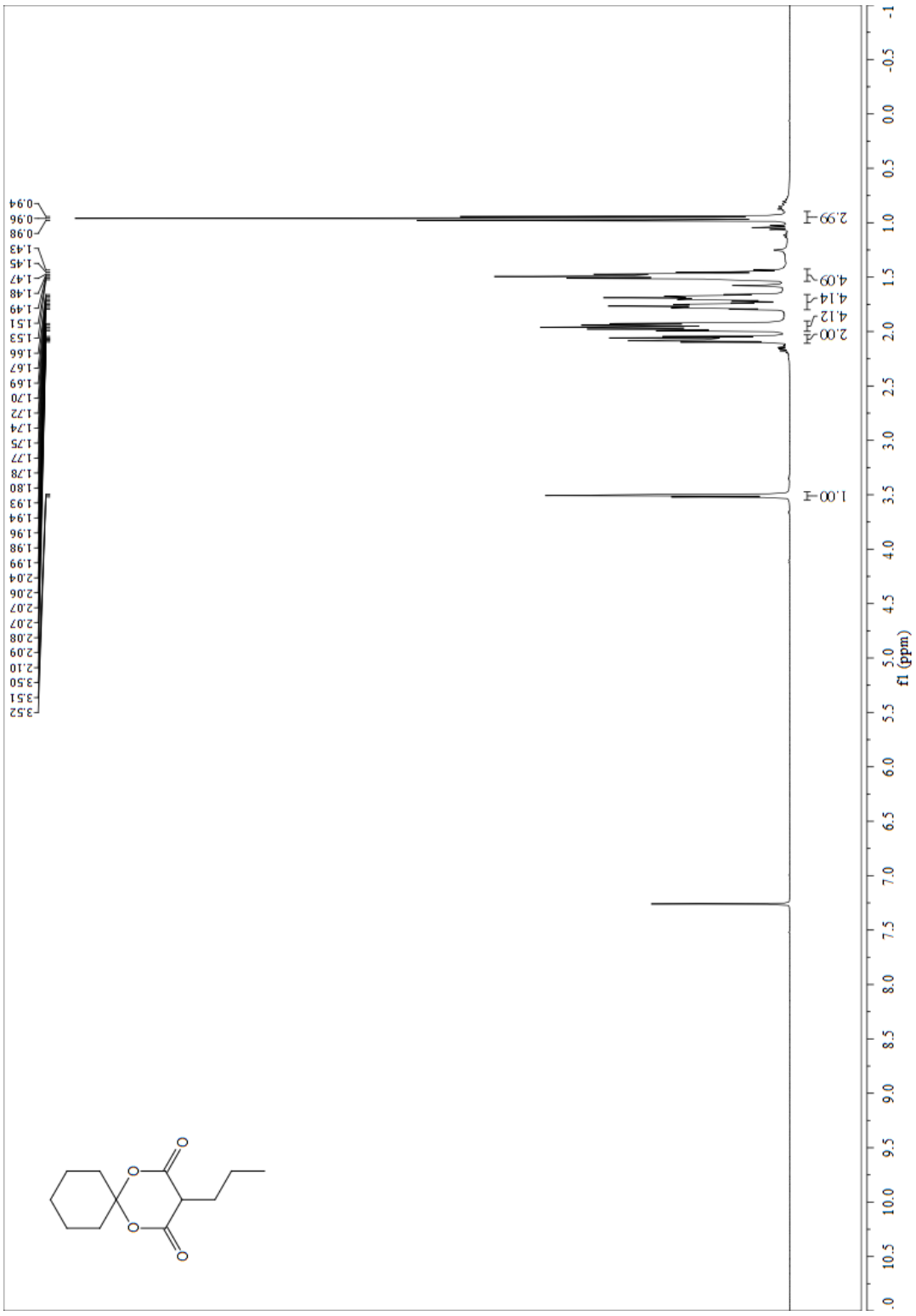
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione



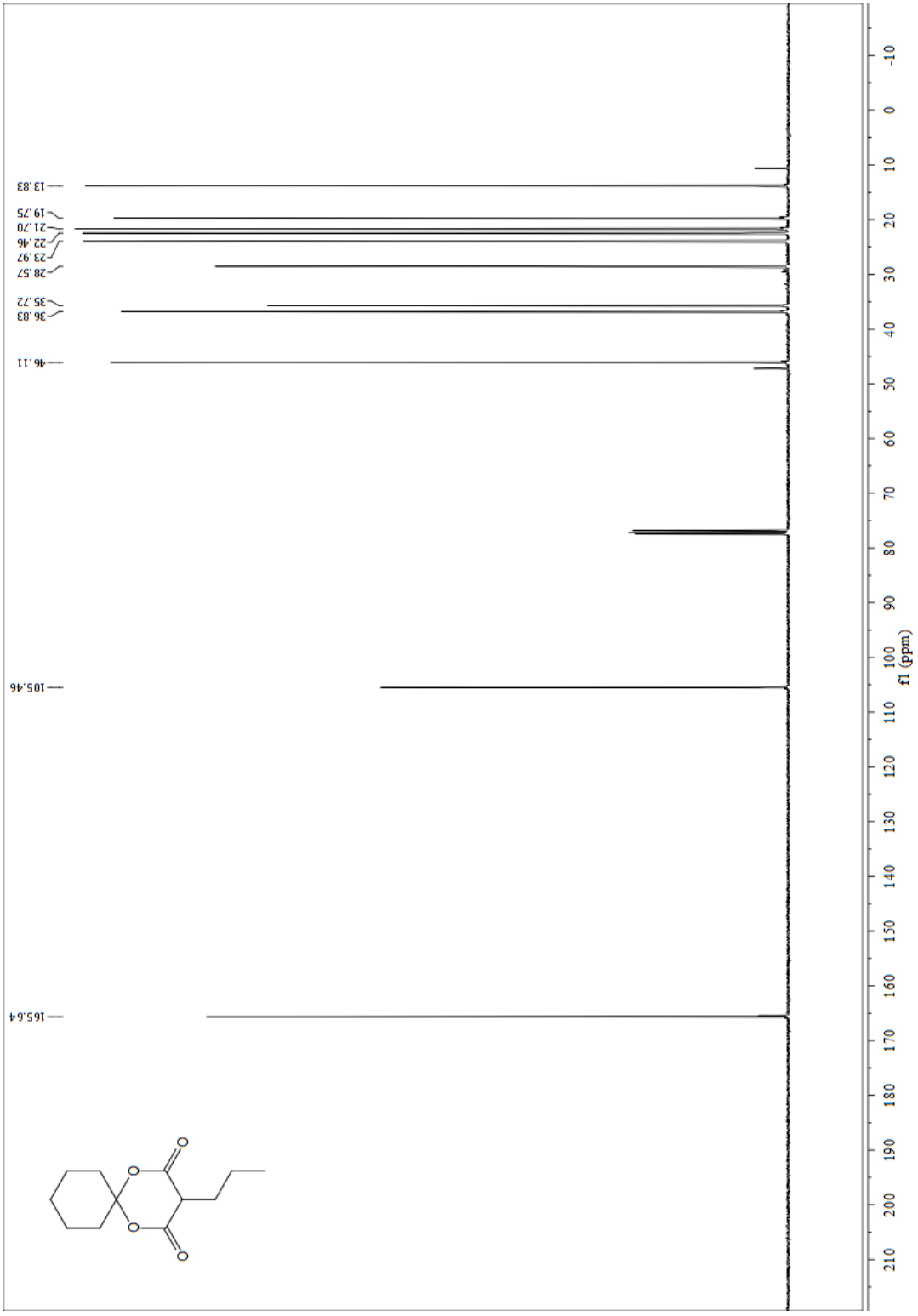
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione



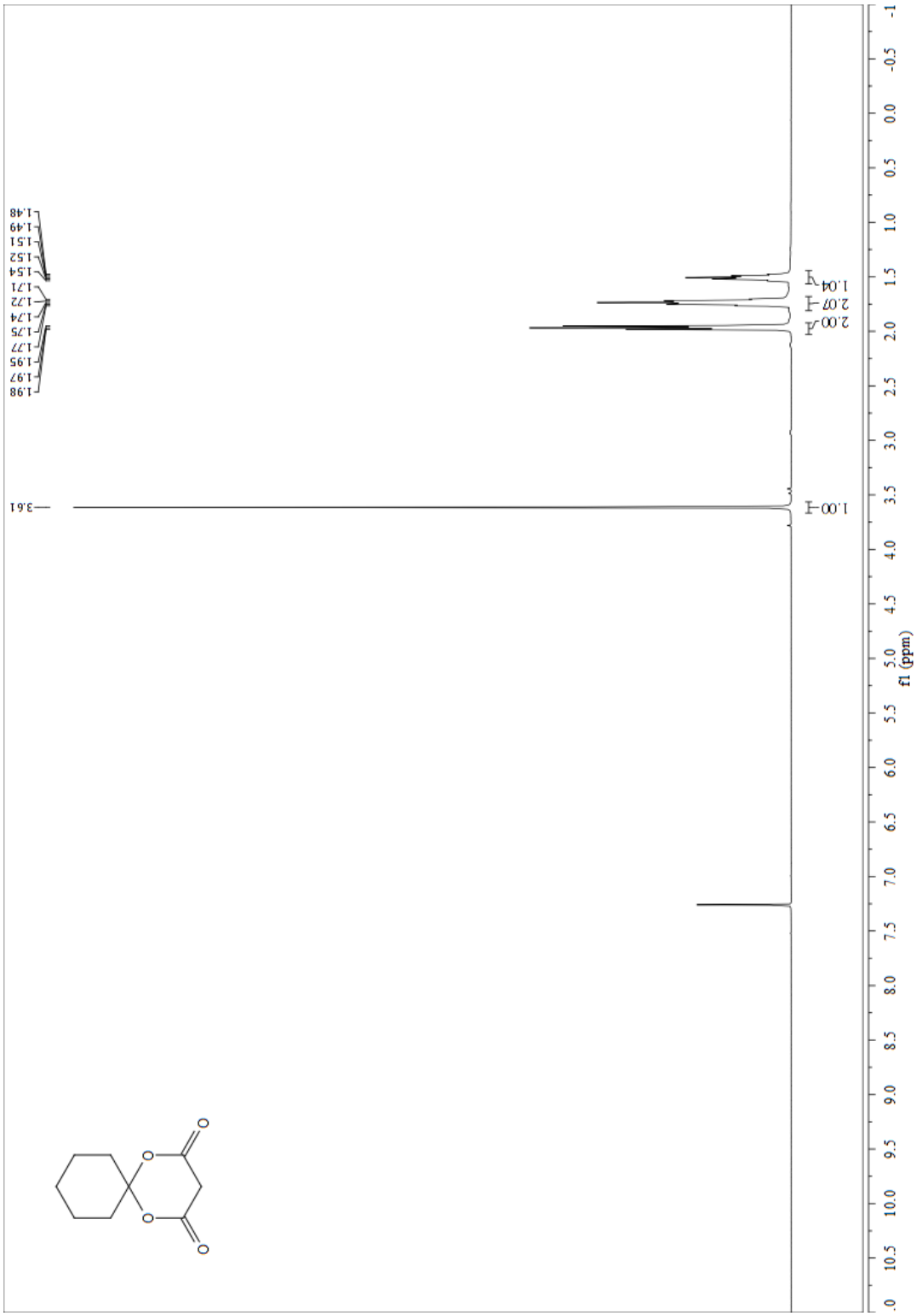
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione



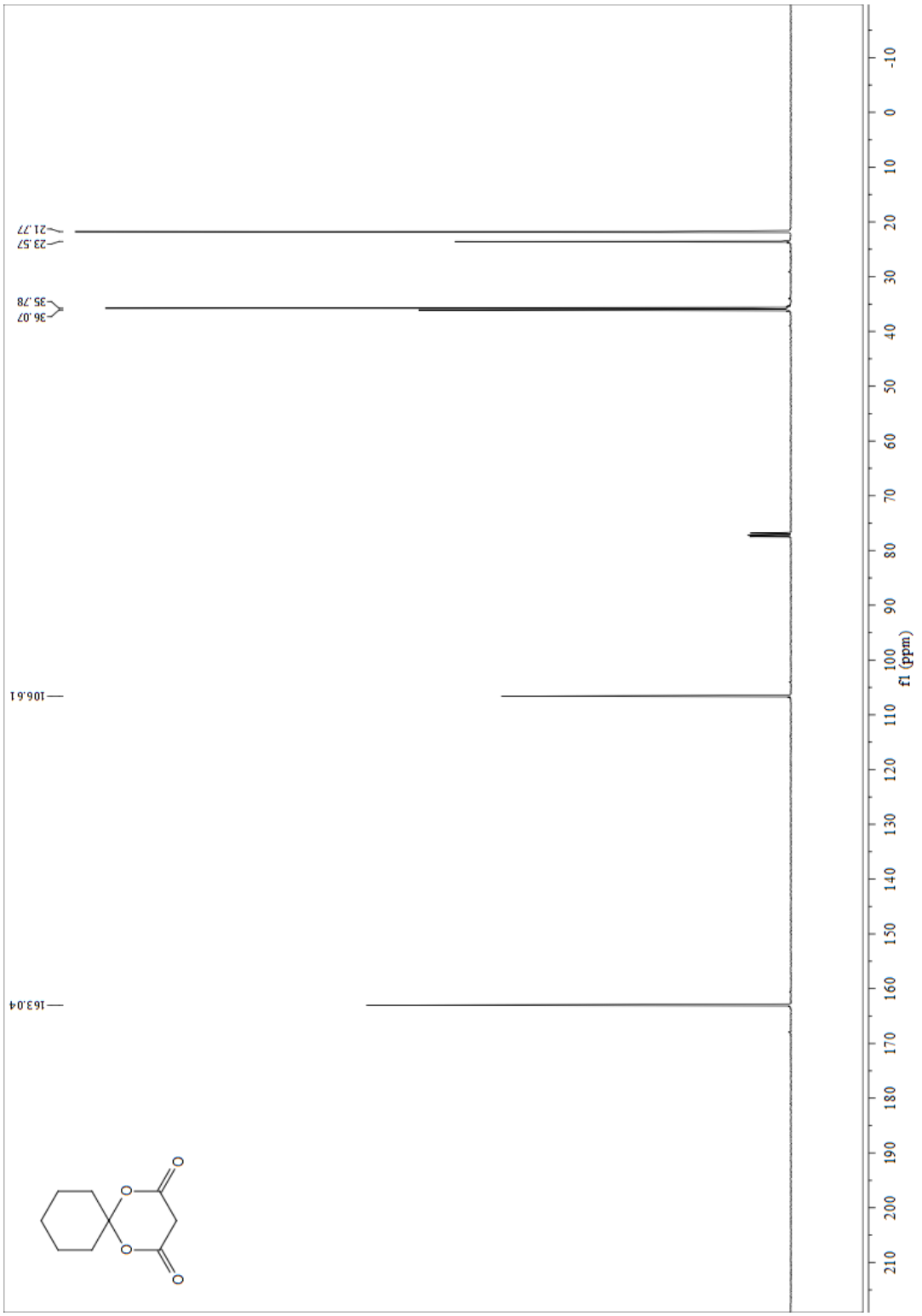
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione



^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 1,5-dioxaspiro[5.5]undecane-2,4-dione (Cyclohexyl-Meldrum's acid)



^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 1,5-dioxaspiro[5.5]undecane-2,4-dione (Cyclohexyl-Meldrum's acid)



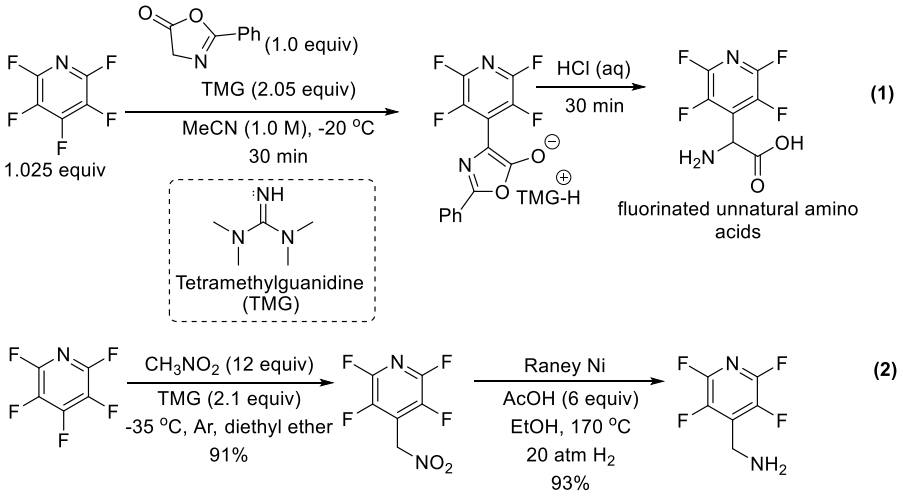
CHAPTER V

SYNTHESIS OF CHLORINATED POLYFLUOROARENES *VIA* CATALYTIC RETRO-HALEX REACTION

5.1 Introduction for the synthesis of chlorinated polyfluoroarenes *via* S_NAr catalysis

In our development of the arylation of Meldrum's acid we came to appreciate the ability of per(poly)fluoroarenes to selectively undergo substitution with *in situ* generated nucleophiles, and soon after our group started looking to exploit the electrophilic nature of aryl fluorides to substitute them with different nucleophiles to ultimately access valuable polyfluoroarenes. In that vein, a nucleophilic substitution reaction between *in situ* generated oxazolone nucleophile and highly fluorinated (hetero)arenes has also been developed in our lab.[111] This reaction provided a rapid and facile access to highly fluorinated non-natural amino acids and derivatives (Scheme 5.1, eq 1). Furthermore, very recently, our group described the substitution of nitronates onto a variety of fluorinated arenes (eq 2). This reaction provides an easy access to perfluoroarylated nitroalkanes which can be followed by a reduction to generate perfluoroarylbenzyl amines in excellent yields.[112] All of the above methods converted cheap and abundant per(poly)fluoroarenes into more valuable and elaborate molecules simply *via* substitution of a

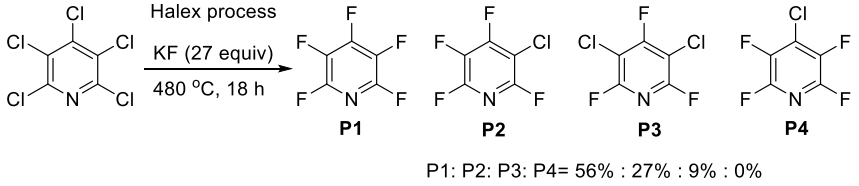
fluoride. As described in Chapter 4, the starting aryl fluorides are made *via* the Halex reaction which is simply a series of substitutions of C–Cl bonds to give C–F bonds.[15] These perchloroarenes are available by exhaustive chlorination of the corresponding proteo-molecule.[113] The recent efforts by our group and others[9a, 86] have dramatically increased the versatility of arylfluorides as starting materials. One missing, but potentially valuable, transformation is halogenation of aryl fluorides. Substitution of a C–F bond with a more labile halogen could allow the products to be used as cross-coupling partners in traditional cross-coupling reactions. Despite the simple nature of halogenated polyfluoroarenes (the halogen can be either I, Br, or Cl), the syntheses of such polyfluoroarenes are not well documented.



Scheme 5.1 Recent S_NAr reactions developed and communicated by the Weaver lab

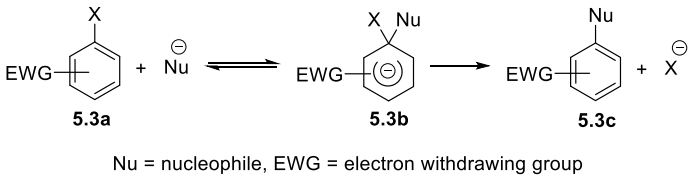
Almost all commercially available mono- and di-chlorofluoroarenes are byproducts of incomplete halogen exchange.[114] Perfluoroarenes are made from a reaction between a fluoride source such as KF and polychloroarenes at a high temperature in a process known as halogen exchange (Halex) reaction.[15, 115] The fluoride anion is reacted on the most activated C–Cl bonds on the molecule.[116] For instance, when pentachloropyridine is reacted with fluoride (Scheme 5.2) a mixture of the perfluoropyridine (**P1**) was obtained, along with 3-chloro-2,4,5,6-

tetrafluoropyridine (**P2**), and 3,5-dichloro-2,4,6-trifluoropyridine (**P3**).[117] It is worth noting that the ability to obtain **P2** and **P3** stems from the fact that the *meta*- position is the least activated on pentachloropyridine. However, one would never be able to obtain the corresponding *para*-chloro product (**P4**) *via* the partial Halex process, because C4 is the first position to undergo substitution. However, if the synthetic strategy is reversed and chlorination of a perfluoroarene is performed (i.e., substitution of a C–F with a C–Cl), it is expected to take place with the same regioselectivity and should give an opportunity to form the previously inaccessible product (**P4**).[116] Due to the potential of accessing previously unavailable regioisomers, as well as the importance of halodefluorinated perfluoroarenes as starting materials, we set out to develop the retro-Halex reaction and efficiently and selectively substitute C–F bonds with chloride.



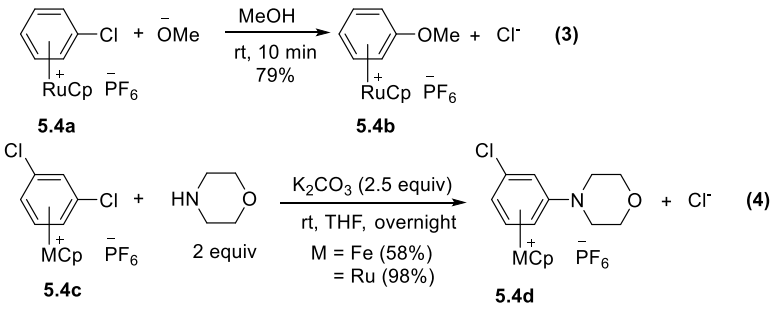
Scheme 5.2 Mixture of products generated by the Halex reaction with pentachloropyridine

The stoichiometric S_NAr of haloarenes is a well-studied class of reactions and the substrates employed in the reaction should contain an activating group (i.e., electron-withdrawing group) to facilitate the reaction (Scheme 5.3).[118] Use of either a nitro or a nitrile group to activate the haloarene is prevalent in the literature.[118a] The S_NAr reaction proceeds though a resonance-stabilized anionic intermediate called the Meisenheimer intermediate (**5.3b**).[119] The electron-withdrawing group stabilizes the negative charge buildup in the Meisenheimer intermediate, and polarizes the C–X bond, facilitating the addition of the nucleophile.[9a]



Scheme 5.3 Typical mechanism for a S_NAr reaction

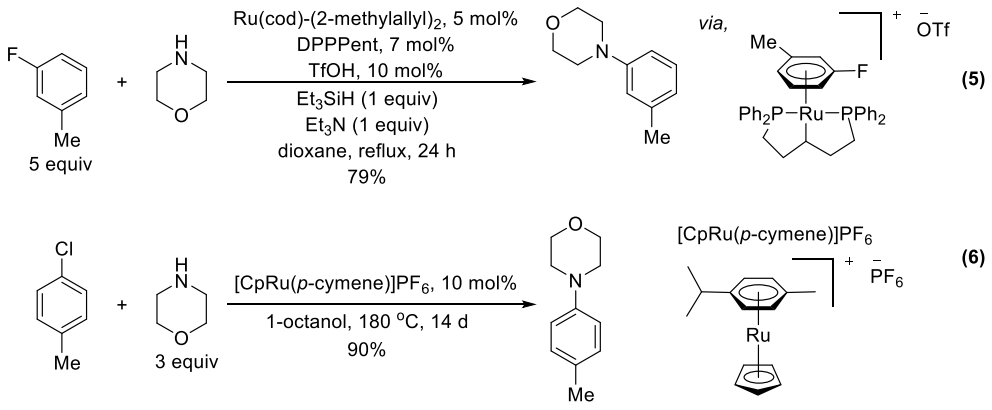
Increases to the scope by use of transition metal reagents to facilitate S_NAr reactions with less activated arene substrates has long been sought, and realized with some success.[120] In this regard, transition metal activations of haloarene C–X bonds toward nucleophilic substitution are achieved *via* a complexation of the π-cloud of the arene to a metal center, which polarizes the substrate (Scheme 5.4).[120a, 121] Conversion of the haloarene into a transition metal η^6 -arene complex (**5.4a** and **c**) requires the use of stoichiometric amounts of transition metals that are attached to the arene. After the reaction that transition metal should be detached from the product which adds an extra step to the synthetic sequence because the η^6-arene–metal bond is relatively strong. Consequently, stoichiometric metal is often required, and liberation of the aryl product is usually carried out by photolysis[122] or oxidation.[123] Due to these drawbacks the use of such methodology has seen limited use in synthesis.



Scheme 5.4 Activation of haloarenes to S_NAr reactions *via* transition metal η^6 -arene complexes

To overcome the above shortcomings of transition metal assisted haloarene activation, catalytic versions of such reactions have emerged. Shibata and co-workers demonstrated the first

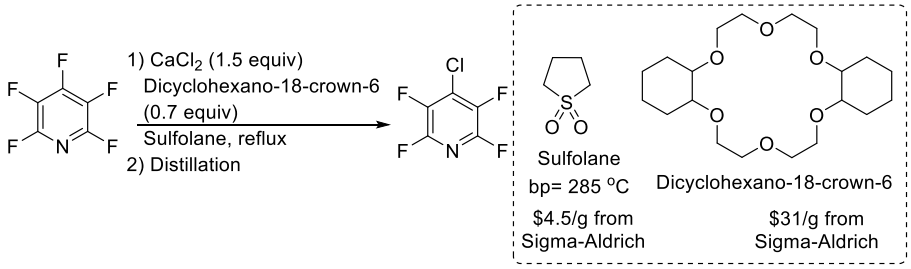
catalytic S_NAr reaction of nonactivated fluoroarenes with secondary amines (Scheme 5.5, eq 5).[118a] The most difficult problem in this catalysis would be the arene exchange step from catalyst-product complex to regenerate the catalyst because of the aforementioned strong metal-arene interaction. To overcome this issue, excess of haloarene is used to provide an imbalance to the equilibrium that facilitates the exchange and drives the reaction forward. As an extension to the above work, Walton and co-workers developed a method to engage unactivated chloroarenes in S_NAr with morpholine (eq 6).[124] Even though, fluorobenzene can undergo substitution with strong nucleophiles such as alkoxides, chlorobenzene itself does not undergo S_NAr.[124] Coordinating the haloarene with the ruthenium center activates the arene toward substitution.



Scheme 5.5 Catalytic SNAr of C–X bonds *via* ruthenium η^6 -arene complexes

However, when compared to arene-Hs, the quadrupole of perfluoroarenes is reversed.[125] For instance, the core of the benzene is negatively charged compared to the periphery while the core of hexafluorobenzene is positively charged compared to its periphery.[125-126] When perfluoroarenes are used as starting materials, it would nearly be impossible to coordinate an electropositive metal to the core of the electron deficient arene, and thus, the above mode of activation is not expected to be feasible.[118a, 124] Therefore, the need exists for an alternative strategy to activate per(poly)fluoroarenes, or more generally electron deficient arenes, towards substitution by weak nucleophiles.

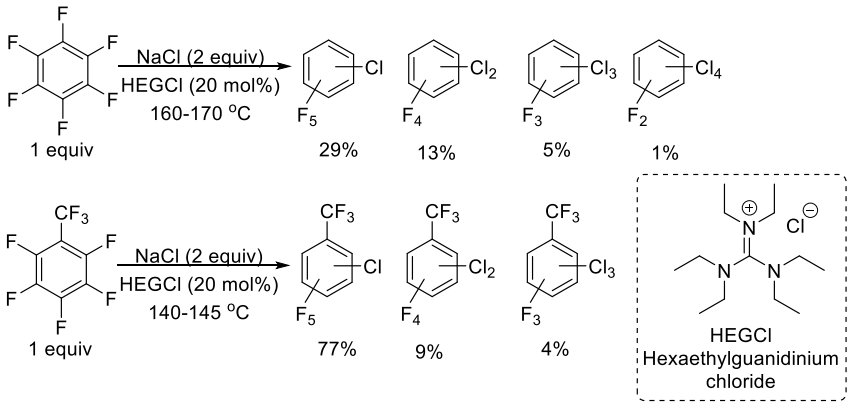
In contrast to rather facile S_NAr addition to C–F bonds by a variety of nitrogen-, oxygen-, and carbon-centered nucleophiles which are prevalent in the literature[9a, 86] the use of chloride as a nucleophile to substitute a C–F with a C–Cl is rather limited. The current technology to perform such transformations use forcing conditions (i.e., refluxing sulfolane, bp = 285 °C) (Scheme 5.6),[127] and consequently, the substrate scope is limited. Furthermore, the method uses relatively expensive solvents and reagents as shown in Scheme 5.6.[128] In addition, the thermodynamics of the transformation present a challenge. The C–Cl bond formed is expected to be weaker than the C–F bond of the starting material (i.e., bond dissociation energies, C_6Cl_6 81.6[129] kcal/mol *vs.* v C_6F_6 145 kcal/mol). Thus, careful consideration of the energetics of the other reagents will be essential if the reaction is to favor the desired chlorinated product. Catalysis of such transformations could reduce the extreme conditions by lowering the activation energy and significantly increase the scope, allowing the retro-Halex to be a synthetically useful strategy.



Scheme 5.6 Current synthetic method of 4-chloro-2,3,5,6-tetrafluoropyridine from pentafluoropyridine[127]

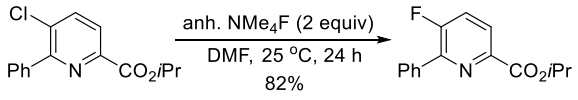
To the best of our knowledge, catalytic reactions to selectively substitute C–F with C–Cl are not known. In 2004, Shipilov[130] and co-workers were able to achieve a retro-Halex of hexafluorobenzene and octafluorotoluene in the presence of catalytic hexaethylguanidinium chloride (Scheme 5.7). Unfortunately, the reaction was unselective and the products were obtained as a mixture of over addition products. Even though, the authors failed to answer the

difficult problem of selective halodefluorination, this work did show the feasibility of catalysis to achieve the goal.



Scheme 5.7 Unselective S_NAr obtained by Shipilov[130]

In 2015, Sanford and co-workers published a mild S_NAr fluorination of heteroaryl chlorides and nitroarenes using anhydrous tetramethylammonium fluoride which operates at room temperature (Scheme 5.8).[118b] The transformation was essentially the reverse of the desired reaction. According to the principle of microscopic reversibility, if a certain series of steps constitutes the mechanism of a forward reaction, the mechanism of the reverse reaction is given by the same steps traversed backwards.[131] In other words the mechanism of a reversible reaction is exactly the same (but reversed) for both the forward and backward version of the reaction. The transition states for each mechanism step are identical regardless of reaction direction. This suggests that the reverse reaction (C–F to C–Cl) might also feasible and should proceed through the same transition state. This led us to explore tetralkylammonium salts as a starting place for the development of the retro-Halex reaction.

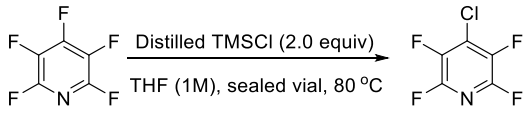


Scheme 5.8 Sanford's room temperature Halex reaction[118b]

5.2 Development of catalytic S_NAr to substitute C–F bonds with C–Cl

We commenced our exploration of the reaction using pentafluoropyridine as the starting perfluoroarene and trimethylsilyl chloride (TMSCl) as the chloride source in THF at 80 °C (Table 5.1, entry1). We chose to use TMSCl because it could serve as a fluoride sponge by forming a strong Si–F bond, and serve as a key thermodynamic driving force (i.e., bond dissociation energies, PhF 127 kcal/mol *vs.* PhCl 97 kcal/mol[23] and H_3SiCl 109 kcal/mol *vs.* H_3SiF 152 kcal/mol[132]). This was expected to make the overall reaction exergonic. However, the reaction failed to produce any product both at 80 °C as well as under microwave irradiation (up to 150 °C). Thus, we concluded that chlorosilane was unable to substitute a C–F bond with a C–Cl without the aid of a catalyst, presumably due to a large activation energy associated with the process.

Table 5.1 Preliminary results of retro Halex reaction



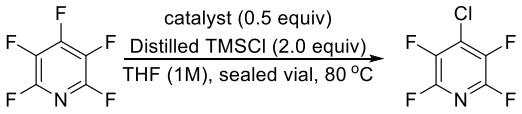
entry	modification	time (h)	conv% to the product
1	None	3/20	no reaction
2	at 150 °C, in a microwave reactor	1	no reaction

As described above, Shipilov[130] observed that hexaethylguanidium chloride can be used to transform a C–F bond with a C–Cl bond. Even though, the method suffers from severe regioselectivity and over addition issues, it hinted the feasibility of the reaction with a properly designed catalyst. There are two transition states (TS) associated with a S_NAr reaction. The first is the nucleophilic addition which leads to a sigma-complex known as the Meisenheimer intermediate, and the second barrier being the decomposition of this intermediate to generate the final product.[116] At this point we contemplated how to decrease the activation energy barrier of the addition step to form the Meisenheimer intermediate. This would be feasible *via* either by

elevating the ground state energy of starting materials or by stabilizing the TS. Therefore, we first attempted to perform a ground state elevation *via* destabilizing the chloride. Formation of a frustrated ion pair[133] was expected to serve the purpose, and thus, increase the nucleophilicity of the chloride.

We started a systematic investigation of the effect of different quaternary ammonium chloride salts that varied in steric size. The results were consistent with the above hypothesis and summarized in the Table 5.2 below. When increasing the size of the ammonium cation the reaction initiated (entry 2). Due to solubility issues, there was no reaction observed when Pr_4NCl was used as the catalyst (entry 3). We were delighted to see a satisfactory conversion of 69% was achieved using Bu_4NCl as the catalyst (entry 4). Furthermore, phosphonium chloride salts also gave the product (entries 5 and 6). It is worth noting that the reaction was completely homogeneous in the presence of Bu_4NCl at 80 ^oC which rules out the possibility of Bu_4NCl to be considered as a phase transfer catalyst alone. The reactions with both Me_4NCl and Et_4NCl were completely homogeneous. If the quaternary ammonium salt acts just as a phase transfer catalyst alone, we should have observed a comparable reactivity with the above two catalysts as the reaction with Bu_4NCl. An absence or a sluggish reactivity of Me_4NCl and Et_4NCl supports the idea that Bu_4NCl is acting in ways beyond a phase transfer catalyst. Nonetheless, we believe that Bu_4NCl serves to increase the concentration of soluble reactive chloride.

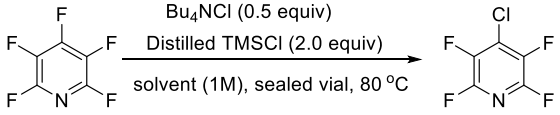
Table 5.2 Attempts to form a destabilized chloride



entry	catalyst	time (h)	conv% to the product
1	Me_4NCl	3/20	NR/NR
2	Et_4NCl	3/20	1/7
3	Pr_4NCl	3/20	NR/NR
4	Bu_4NCl	3/20	7/69
5	$H_3C(H_2C)_5-\overset{(CH_2)_5CH_3}{\underset{(CH_2)_5CH_3}{P^+}}-(CH_2)_{13}CH_3Cl^-$ instead of NBu_4Cl	3/20	3/63
6	Ph_4PCl instead of Bu_4NCl	3/20	NR/<2%

Next, we attempted to find the best solvent for the chlorodefluorination (Table 5.3). Among all the other solvents tried, only DMF yielded the product, albeit only sluggishly. However, halogenated solvents and nonpolar aromatic toluene provided no reaction. Therefore, THF was chosen as the solvent for further optimizations.

Table 5.3 Solvent screening for chlorination reaction

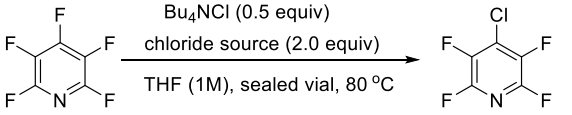


entry	solvent	time (h)	conv% to the product
1	THF	3/20	7/69
2	DMF	3/20	3/20
3	MeCN	3/20	NR/<2
4	DCM	3/20	NR/NR
5	Toluene	3/20	NR/NR

Finding a cheaper and easier to handle chloride source would be important in any large scale syntheses. To this end, some inexpensive inorganic chloride sources were screened (Table 5.4). Interestingly, all the inorganic chlorides gave the product and $CaCl_2$ even provided a

superior reactivity when compared to TMSCl despite of the heterogeneity of the reaction mixture. However, it was excluded from further optimizations due to limitations of substrate scope which gave either no or sluggish reaction with some less activated perfluoroarenes. For instance, $CaCl_2$ yielded the product with pentafluoronitrobenzene and pentafluoropyridine but not with pentafluoroacetophenone. In contrast, TMSCl did not seem to have this limitation. Therefore, we chose to use TMSCl as the chloride source for further optimizations.

Table 5.4 Reaction with different chloride sources



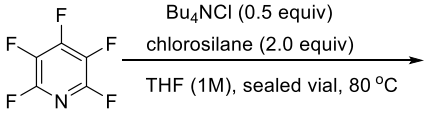
entry	chloride source	time (h)	conv% to the product
1	TMSCl	3/20	7/69
2	KCl	3/20	20/25[a]
3	NaCl	3/20	45/75[b]
4	$BaCl_2.2H_2O$	3/20	19/55
5	$CaCl_2$	3/20	32/79

[a]another 49% of byproduct observed by ^{19}F NMR
[b]another 20% of byproduct observed by ^{19}F NMR

As discussed above, a silane was used to make the reaction exergonic. Presumably, the major role of the silane occurred after collapse of the Meisenheimer complex, in which it was anticipated to soak up the fluoride and regenerate the chloride. Therefore, when we investigated the effect of different chlorosilanes on the rate of the reaction, our observations were surprising. If the addition of chloride is the rate determining step (RDS), the latter step involving the silane would not be expected to have an effect on the reaction rate. When we performed our S_NAr with a few chlorosilanes (Table 5.5), the reaction was faster with both dimethylchlorosilane and diphenylchlorosilane. However, reduction of the carbonyl group was observed when perfluoroacetophenones were used as substrates. Due to this limitation and the fact that it is inexpensive, TMSCl was determined to be the optimum chlorosilane. The reason for the

unexpected effect of chlorosilane structure on the rate was further explored and is presented in the discussion of the mechanistic investigation.

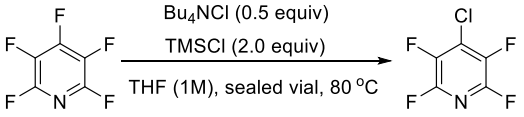
Table 5.5 Effect of chlorosilane on the reaction rate



entry	chlorosilane	time (h)	conv% to the product
1	TMSCl	3/20	7/69
2	Me_2SiHCl	3/20	85/100
3	Ph_2SiHCl	3/20	85/100
4	*t*-$BuMe_2SiCl$	3/20	5/33

Finally, we looked at the effect of temperature and effect of added water (Table 5.6). The reaction was significantly slowed down when the temperature was lowered to 45 °C from 80 °C, and no product formation was observed at room temperature (entries 1-3). Water was intentionally added to dry THF which was then used as the solvent, to assess the importance of dry reagents. The inclusion of water had a deleterious effect on the reaction, even when used in substoichiometric amounts. One partial explanation might be that the water facilitated the hydrolysis of TMSCl. However, given that 2.0 equivalents of TMSCl were used, this cannot fully explain the retardation of the rate. Thus, 80 °C was chosen as the optimal temperature to run the reaction, and all the reagents were dried prior to their use in the reaction.

Table 5.6 Effect of temperature and wetness

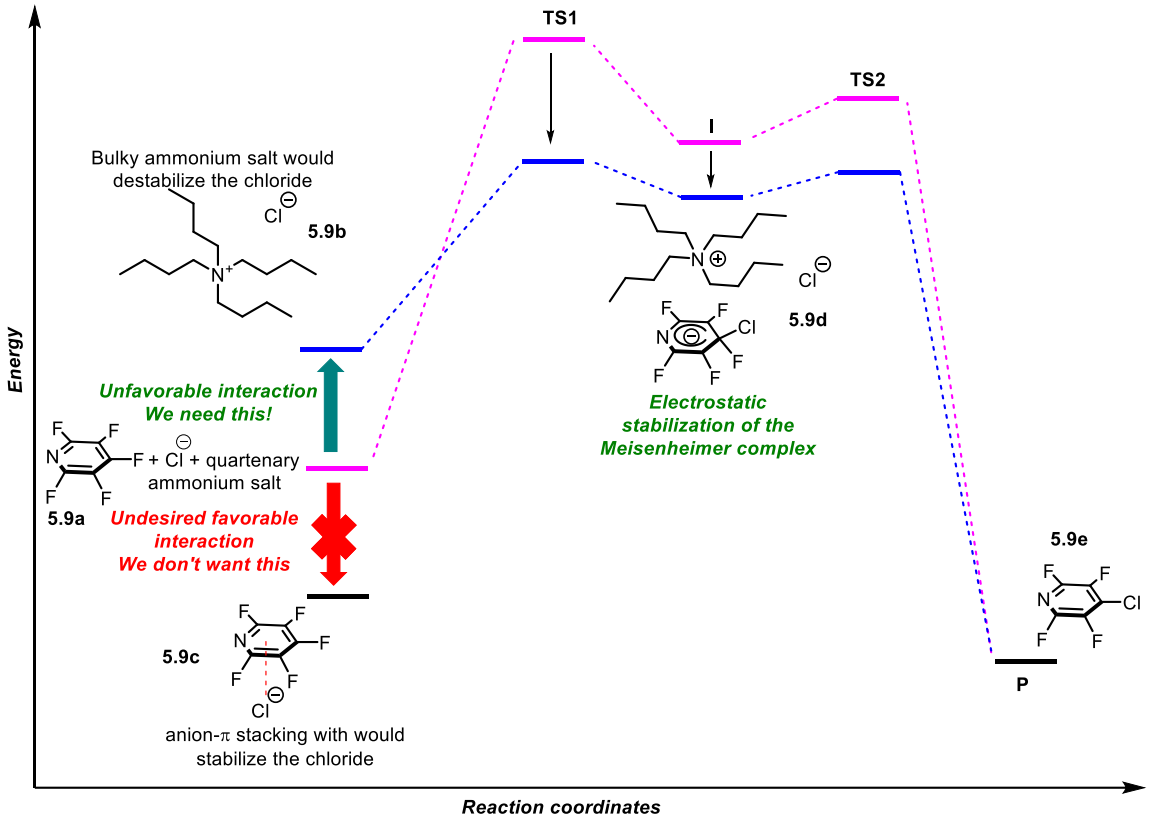


entry	modification	time (h)	conv% to the product
1	at rt	3/20	NR/NR
2	at 45 °C	3/20	NR/5
3	none	3/20	7/69
4	with 20 mol% H_2O	3/20	3/28
5	with 50 mol% H_2O	3/20	2/17
6	with 100 mol% H_2O	3/20	1/10

As discussed above, we achieved a moderate reactivity when we used bulky Bu_4NCl in the reaction. Presumably, this facilitated the reaction by destabilizing of the chloride nucleophile. Specifically, the chloride is not well solvated because of the anhydrous conditions, and because the balancing cation is a diffuse ammonium salt, the chloride is expected to form a frustrated ion pair. Furthermore, we expected that the cationic ammonium salt also electrostatically stabilized the negatively charged Meisenheimer intermediate (Scheme 5.9), further enhancing the rate of the reaction. According to Hammond's postulate,[134] the stabilization of an intermediate which is near the TS would lower the energy barrier of the nearby TS, and thus, it would also serve to lower the TS energy of the chloride addition step.[87]

It is worth noting that there can be another molecular interaction that is expected to hinder the reaction, namely, the interaction between the perfluoroarene and the chloride ion can form an anion-π interaction[135] as shown in Scheme 5.9 (**5.9c**). This is a well-documented interaction that stems primarily from the favorable electronic interaction between the negatively charged chloride with the positively charged quadrupole of the perfluoroarene, and is of appropriate size to maximize these interactions.[136] Because the anion-π interaction is stabilizing,

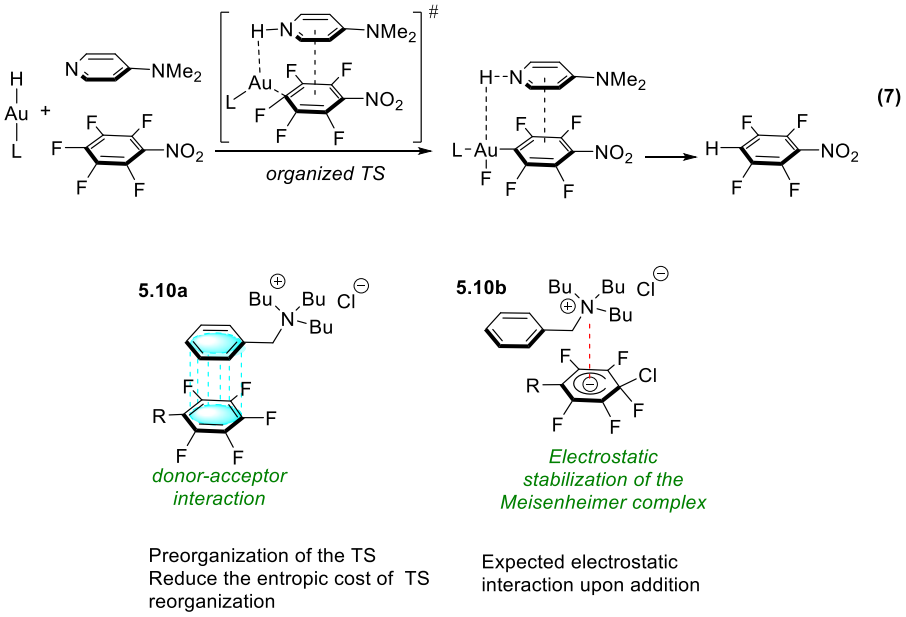
it would decrease the energy of the ground state, and consequently, will result in an increase in the activation energy associated with chloride addition to the perfluoroarene.



Scheme 5.9 Possible, simplified energy diagram for catalytic chlorination

At this point we turned our attention to the activation of the perfluoroarene towards nucleophilic addition. As discussed above, we believed that the ammonium was serving to stabilize the Meisenheimer intermediate. However, we also expected that prior to the chloride addition to the perfluoroarene there would be no attractive interaction between the neutral perfluoroarene and the ammonium cation. Thus, in order for the ammonium to stabilize the negatively charged intermediate, a significant amount of molecular reorganization would be required. Consequently, we believed that preorganization of the perfluoroarene near the catalyst would help to overcome the entropic cost of the reaction. It has been shown that perfluoroarenes (as electron acceptors) can interact with H-arenes (as electron donors), in which the HOMO of the

electron rich arene-H interacts with the LUMO of the electron poor perfluoroarene, and is known as a donor-acceptor complex. This interaction has been used to organize transition states. Zhang has elegantly exploited this feature, and shown that perfluoarenes (as electron acceptors) can interact with H-arenes (as electron donors) and can be used to organize transition states which then facilitated the hydrodefluorination of perfluoroarenes as shown in Scheme 5.10 (eq 7).[137] We hypothesized that tethering an arene group to the quaternary ammonium salt could lead to a donor-acceptor complex with the perfluoroarene and could bring the perfluoroarene into close proximity with the positively charged ammonium ion. Thus, less molecular reorganization would be needed to stabilize the intermediate, resulting in a TS barrier reduction to form **5.10b**.



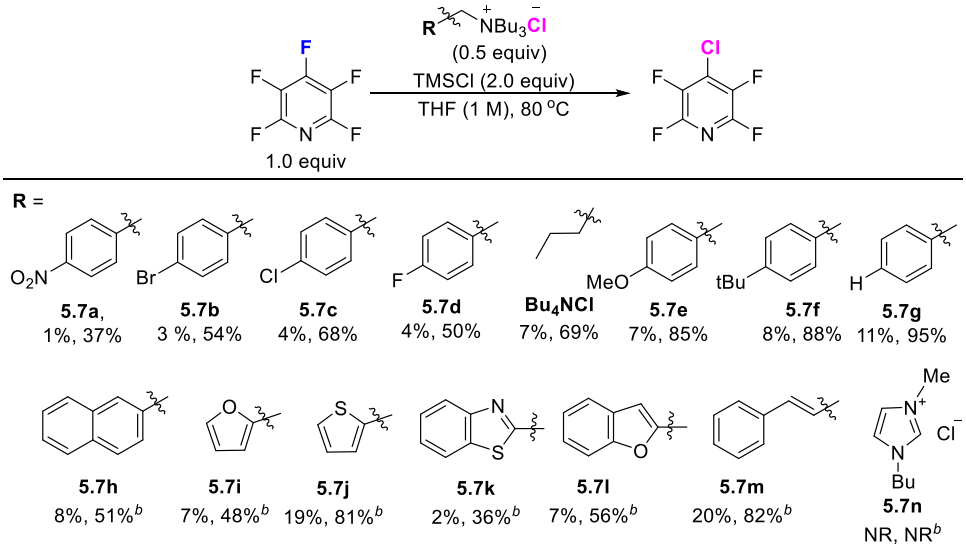
Scheme 5.10 Expected beneficial interactions in the catalytic cycle

To this end, we screened commercially available benzyltributylammonium chloride ($BnNBu_3Cl$) as well as a number of analogs we synthesized (Table 5.7). At the outset, it should be noted that all the reactions were completely homogeneous, which allows us to rule out solubility as a factor. In order to test both electronic and steric effects, the reaction was carried out with series of electron withdrawing (**5.7a-d**), electronic donating (**5.7e**, **f**), neutral (**5.7g**) and

sterically demanding (**5.7f**) groups on the arene. Additional screening with some heteroaryl (**5.7i-l**) and styrenyl derivatives with extended conjugation (**5.7m**) was also performed. Catalyst **5.7n** gave us an important insight to the reaction. If stabilization of the Meisenheimer intermediate[119] was the only important feature, then it could be expected that catalyst **5.7n** would have worked. The lack of reactivity hinted that other features were also important to facilitating the reaction.

The catalyst screen revealed that catalysts containing electronically neutral (**5.7f**) and donating (**5.7e**, **f**) arenes gave superior results when compared to the tetra-alkylammonium cation devoid of an arene (95% *vs.* 69% conv. after 20 h for $BnNBu_3Cl$ and Bu_4NCl). Meanwhile, sluggish reactions were observed when the benzyl fragment contained electron withdrawing groups (**5.7a-d**). These observations are consistent with, and support the idea of an aromatic donor-acceptor interaction between the arene of the catalyst and the perfluoroarene being used to organize the transition state and facilitate the reaction.[138] Among the other salts tested, only **5.7j** and **5.7m** offered comparable conversions to Bu_4NCl. After achieving substantial improvement using commercially available $BnNBu_3Cl$ (**5.7g**), we decided to proceed using $BnNBu_3Cl$ as the catalyst.

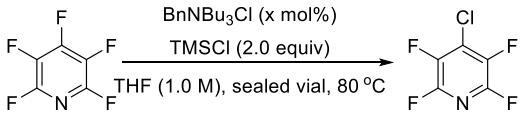
Table 5.7 Catalyst screen for catalytic halodefluorination



[a] %convesion detrmined after 1 h, 20 h by ^{19}F NMR, [b] %convesion detrmined after 3 h, 20 h by ^{19}F NMR

We next examined the catalyst loading. As expected, amount of the catalyst had a direct relationship with the rate of the reaction as shown in Table 5.8. Unfortunately, the catalyst displayed a relatively low TON of ~3-4. One explanation of the low TON is catalyst deactivation/decomposition during the reaction. Alternatively, the involvement of more than one catalyst molecule in the catalytic cycle could also necessitate higher catalyst concentrations, and consequently give the appearance of low TON. However, with lower catalyst loadings such as 10 mol% or 25 mol%, the reaction never reached completion even after prolonged reaction times (i.e., some starting material always remained unreacted) (entry 1-2). Careful evaluation of the crude reaction at about 90% conversion revealed a significant formation of benzyl chloride. Presumably, the source is the decomposition of $BnNBu_3Cl$ catalyst. Thus, we used 0.4 equiv for the substrate screening to ensure reaction completion in reasonable reaction times, and while this loading is relatively high we were not dissuaded given the inexpensive nature of the catalyst. The nature of the catalyst was further explored and will be discussed more, later in this chapter.

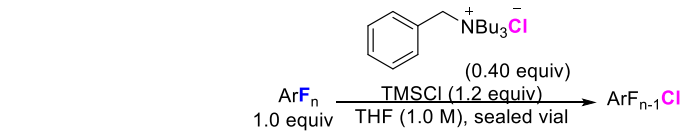
Table 5.8 Catalyst loading experiment

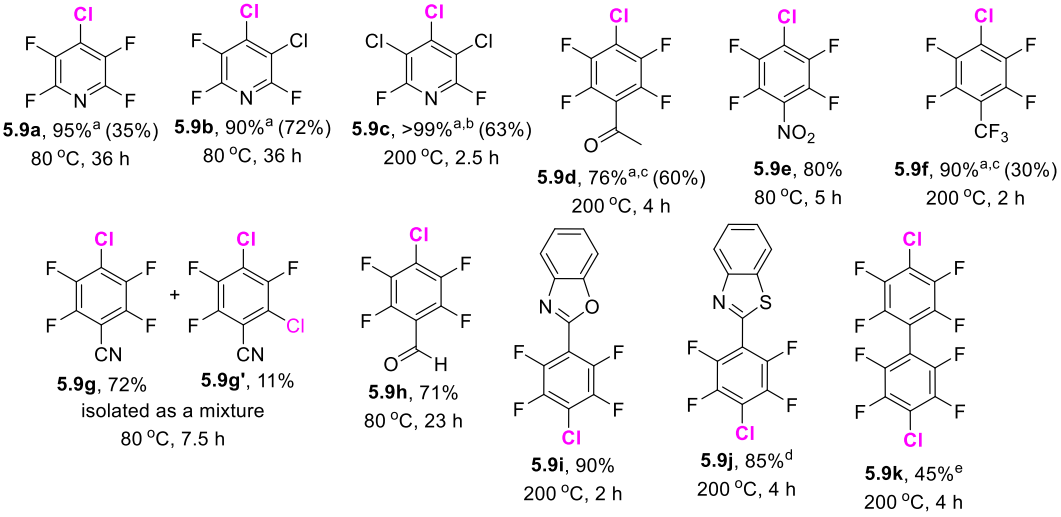


entry	catalyst loading	time (h)	conv% to the product
1	10 mol%	3/40	<1/30
2	25 mol%	3/40	18/>95
3	40 mol%	3/40	25/100
4	50 mol%	3/40	30/100

With optimum conditions in hand, we next evaluated the scope of the reaction (Table 5.9). The reaction proceeded with good to excellent yields, and we were able to obtain clean reaction profiles in most of the cases. In contrast to the incomplete Halex which provides access to *meta* chlorinated polyfluoropyridines, in contrast this method provides access to the complimentary *para*-chlorofluoroarene products with excellent regioselectivity, providing access to new fluorinated derivatives. Specifically, **5.9a-c** have never been synthesized prior to our work. Consistent with the S_NAr reaction in which the addition of the nucleophile is the difficult step, faster reactions were observed with the perfluoroarenes bearing electron withdrawing groups such as nitro (**5.9e**), nitrile (**5.9g**), and aldehyde (**5.9h**), though less activated or unactivated substrates could also be engaged simply by elevating the temperature (**5.9f** and **k**). By simply increasing the amounts of TMSCl and $BnNBu_3Cl$ selective dichlorination of decafluorobiphenyl was achieved (**5.9k**). The reaction showed a satisfactory functional group compatibility including ketones (**5.9d**), trifluoromethyl compounds (**5.9f**), aldehydes (**5.9h**), and especially some heteroaromatics (**5.9i-j**). Overall, compared to the existing technology, we satisfactorily accomplished the goal of carrying out the chlorodefluorination with good regioselectivity and under a significantly milder temperature conditions. Specifically, in a previous report pentafluoropyridine was reacted at 285 °C[127] and we reduced it to 80 °C. This temperature reduction is important for functional group tolerance.

Table 5.9 Reaction scope for the catalytic retro-Halex reaction

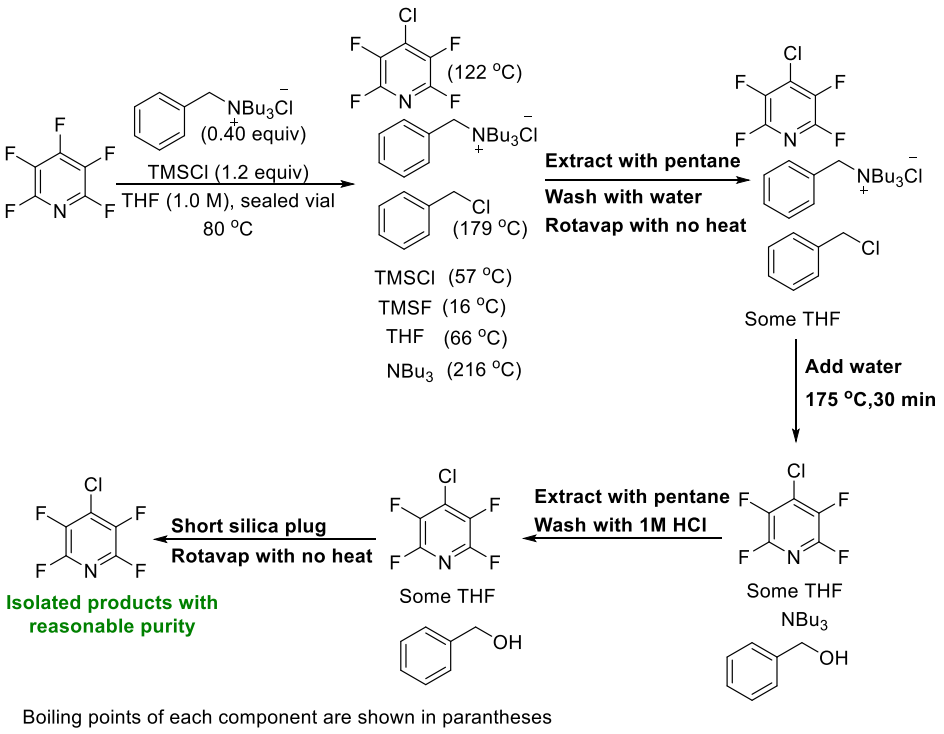




[a] NMR yield (isolated yield after workup in paranthesis), [b]Used $BnNBu_3Cl$ (1.0 equiv) and TMSCl (2.0 equiv), [c]Used $BnNBu_3Cl$ (0.5 equiv) and TMSCl (2.0 equiv), [d]Used $BnNBu_3Cl$ (0.8 equiv) and TMSCl (2.0 equiv), [e]Used $BnNBu_3Cl$ (1.0 equiv) and TMSCl (2.4 equiv)

While this work was interesting from a catalysis development standpoint, we envisioned the products of the catalytic chlorodefluorination will serve as starting materials for further couplings, and therefore must truly be accessible. Due to the reduction of van der Waals interaction, per- and polyfluoroarenes tend to be far more volatile than their molecular weight would suggest, i.e. they are quite volatile, the boiling point of **5.9a** is around 122 °C.[127] Therefore, we needed to develop an isolation strategy that would allow the isolation of the volatile products and allow us to take advantage of the new-found reactivity. Therefore, our isolation method began by selective extraction of the product into a nonpolar solvent (pentane) after decomposing the remaining catalyst and remaining starting materials (Scheme 5.11). After the reaction was completed, the reaction vial was uncapped allowing the removal of volatile TMSF (bp = 16 °C). The reaction was then taken up in pentane and the remaining TMSCl was hydrolyzed by adding water. Separation of the pentane layer followed by washing with water

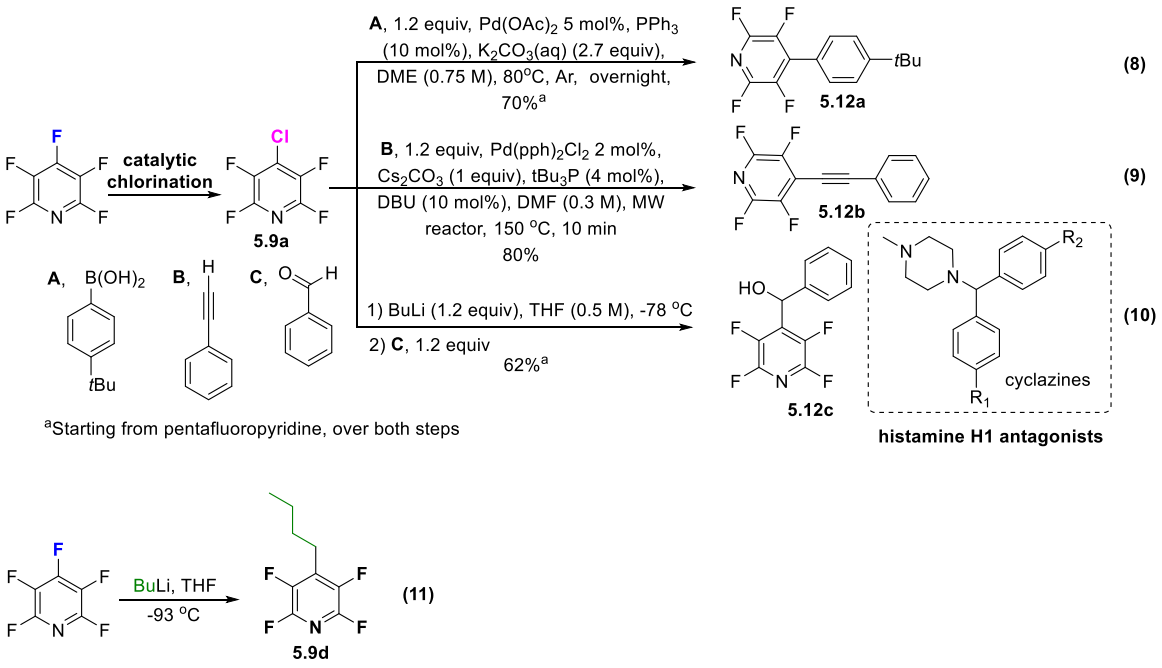
removed a significant amount of THF (solubility of THF, 0.3 g/ 1 g of water[139]) and polar products stemming from the hydrolysis of TMSCl. Remarkably, substantial amounts of the ammonium salt remained in the pentane layer after washing with H_2O. Thus, the remaining catalyst was decomposed to NBu_3 and benzyl alcohol by heating the crude mixture in the presence of water at 175 °C. Then, an HCl wash was employed to protonate the NBu_3 and remove it from the organic layer. Finally, the crude product was passed through a short plug of silica and eluted with a minimal amount of pentane, which allowed the removal of the polar benzyl alcohol, and the organic layer was rotavaped with no heat to obtain the desired products which are pure enough to perform further coupling reactions.



Scheme 5.11 Workup method for the isolation of volatile chlorodefluorinated products

To show the versatility of chlorofluoroarene products, we subjected them to coupling reactions that would be difficult, or not possible, with the fluoroarene starting materials (Scheme 5.12). Namely, we performed Suzuki[140] (eq 8) and Sonogashira[141] (eq 9) coupling reactions of

5.9a, which proceeded smoothly to make **5.12a** and **5.12b** in good yields. Pentafluoropyridine is known to undergo substitution with lithiates[142] to form the corresponding alkylated products (eq 11) due to the electrophilic nature of the aryl fluoride. However, after chlorinating pentafluoropyridine, the product **5.9a** underwent halogen-lithium exchange, and gave smooth addition to benzaldehyde yielding **5.12c** (eq 10). Diaryl methanols have been used to access bioactive molecules, so it is conceivable that **5.12c** could potentially be used as a route to fluorinated analogs of such bioactive molecules.[143] These reactions demonstrate the potential of catalytic chlorodefluorination to be a straightforward method to access fluorinated starting materials with which traditional coupling reactions can be used to make functionalized per(poly)fluoroarenes. Thus, this method helps us accomplish our overall objective of increasing synthetic access to multifluorinated arenes.



Scheme 5.12 Synthetic utility of chlorodefluorinated products

As a part of the development of a catalytic chlorodefuorination, we wanted to understand the mechanism and phenomena which lead to the catalysis and specifically the observed rate

enhancement when $BnNBu_3Cl$ was used compared to NBu_4Cl. Recall that the structure of the catalyst had a phenomenal effect on the rate of the reaction (95% *vs.* 69% conv. after 20 h for $BnNBu_3Cl$ and Bu_4NCl respectively). We postulated that an aromatic interaction between the arene moiety of the catalyst and the perfluoroarene, along with electrostatic interactions between negatively charged Meisenheimer intermediate and the positively charged ammonium moiety of the catalyst were responsible for the dramatic rate enhancement of the reaction.

Formation of donor-acceptor complexes between electron rich arenes and electron poor fluoroarenes is prevalent in literarure.[144] We postulated that such an interaction could also occur between the perfluoroarene and the phenyl moiety of the catalyst. When this happens, the HOMO-LUMO gap becomes smaller resulting a new red shifted absorption band which may be observed *via* UV-Vis spectroscopy.[137, 144a] To observe this phenomenon, separate UV-Vis spectra were obtained by mixing 1) pentafluoronitrobenzene (PFNB): $BnNBu_3Cl$ in 1:1 molar ratio, 2) PFNB: $BnNBu_3Cl$ in 1:2 molar ratio in THF, and then those were compared to the UV-Vis spectra of the individual components. Comparison of those mixtures with the spectra of the individual components revealed the emergence of a new weak red shifted absorption band around 370-380 nm (Fig. 5.1, (a)). This is consistent with a formation of a donor-acceptor complex.[137] Overlap of PFNB's absorption band with the newly formed band obscures the direct identification of the maximum absorption wavelength (λ_{max}). However, a first derivative analysis of the UV-Vis curves allowed us to identify a new red-shifted λ_{max} of both the 1:1 and 2:1 catalyst:PFNB complexes (Fig. 5.1, (b)). The observation of two different λ_{max} values suggests the formation of two distinct types of complexes. The absorption curves and the first derivative analysis are shown in Figure 5.1.

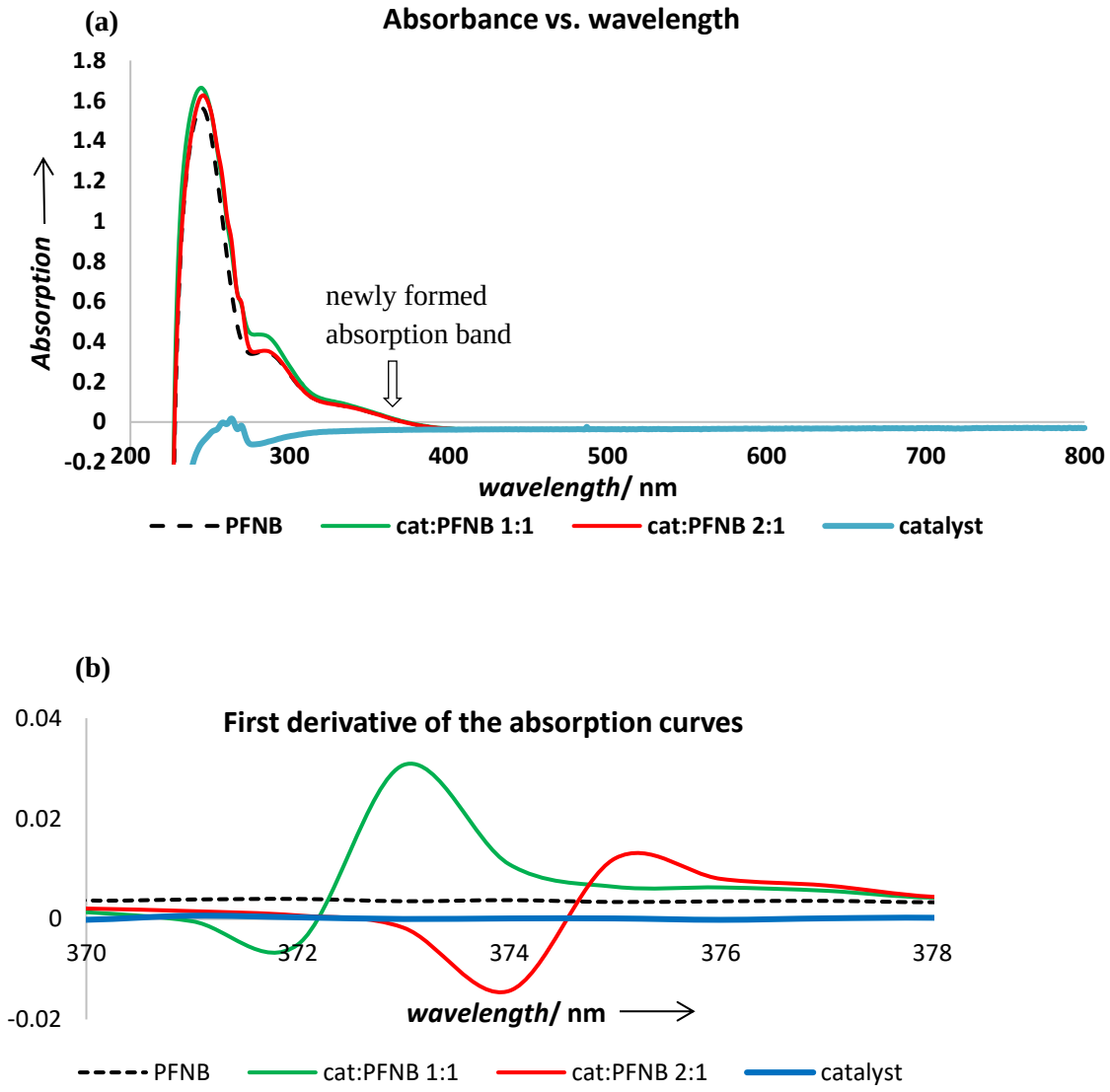


Figure 5.1 (a) UV-Vis spectra for the formation of a donor-acceptor complex between PFNB and $BnNBu_3Cl$, (b) First derivative analysis showing the presence of two types of complexes

In order to strengthen the evidence of a donor-acceptor interaction, an NMR titration experiment was carried out using pentafluoropyridine (PFP) and $BnNBu_3Cl$ using $CHCl_3$ as the solvent. Importantly, at room temperature no appreciable reaction occurs, allowing us to study the interactions of the molecules. Two separate stock solutions of $BnBu_3NCl$ and PFP were

prepared. In eight separate NMR tubes, the above two solutions were added in such a way that each tube contained a fixed amount of $BnBu_3NCl$ and varying amounts of PFP (from 0.0 equiv. to 4.0 equiv.). The reactions were monitored by ^{19}F NMR for chemical shift changes of PFP. Interestingly, we observed up-field shifts of the fluorines signals with increasing $BnNBu_3Cl$ concentration up to about 0.85 equivalents, consistent with shielding of the fluorines on pentafluoropyridine. Presumably, this occurred as a result of the interaction with the electron rich phenyl ring of $BnNBu_3Cl$ (Fig. 5.2). However, between 0.85 - 2.0 equivalents, the fluorine signals moved downfield. Finally, after 2 equivalents of $BnNBu_3Cl$, the ^{19}F chemical shifts became constant. These results are consistent with initial formation of a 1:1 and then a 1:2 complex between the fluoroarene and the catalyst, which results in more deshielding of the fluorines.

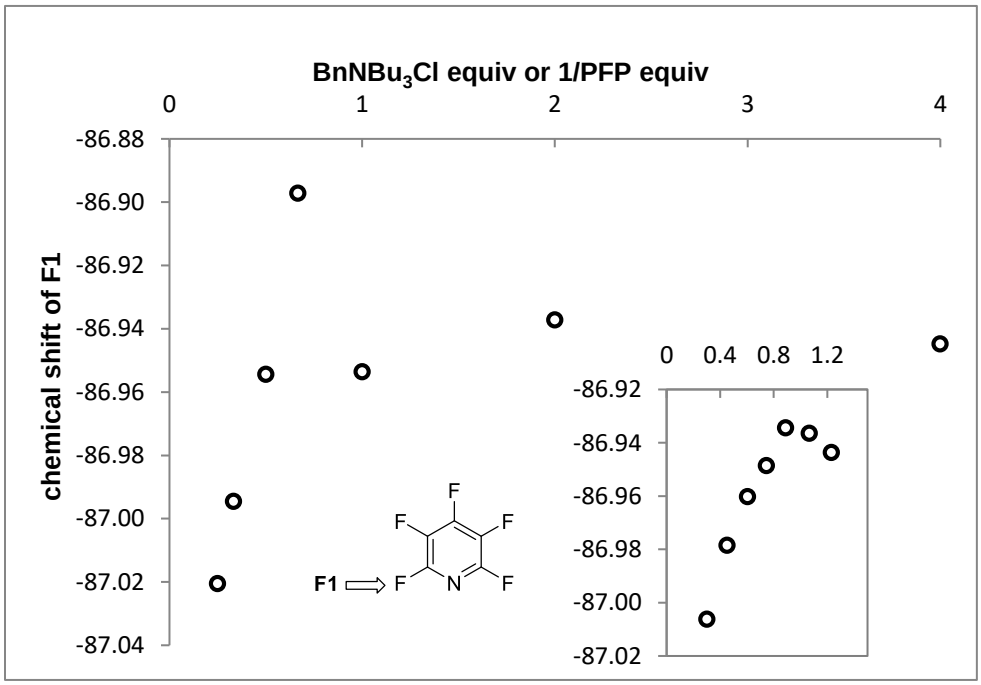


Figure 5.2 ^{19}F NMR spectra of the titration between pentafluoropyridine and $BnNBu_3Cl$

We further confirmed the occurrence of a 1:2 complex between perfluoroarene:$BnNBu_3Cl$ by performing a kinetic analysis using the initial rates method. To

show the rate dependency of the reaction on the catalyst loading, the catalytic chlorodefluorination reaction was carried out with different amounts of catalyst. Calculated initial rates as a function of the catalyst loading is shown below in **Table 5.10**. The order of the reaction was then calculated as follows.

Initial rate = k [cat]^{a}

After 4 h,

With 0.04 equiv catalyst, rate = 0.25= k [0.04] ^{a}

With 0.08 equiv catalyst, rate = 1.25= k [0.08] ^{a}

Order of the reaction with respect to the catalyst (a) = 2.3

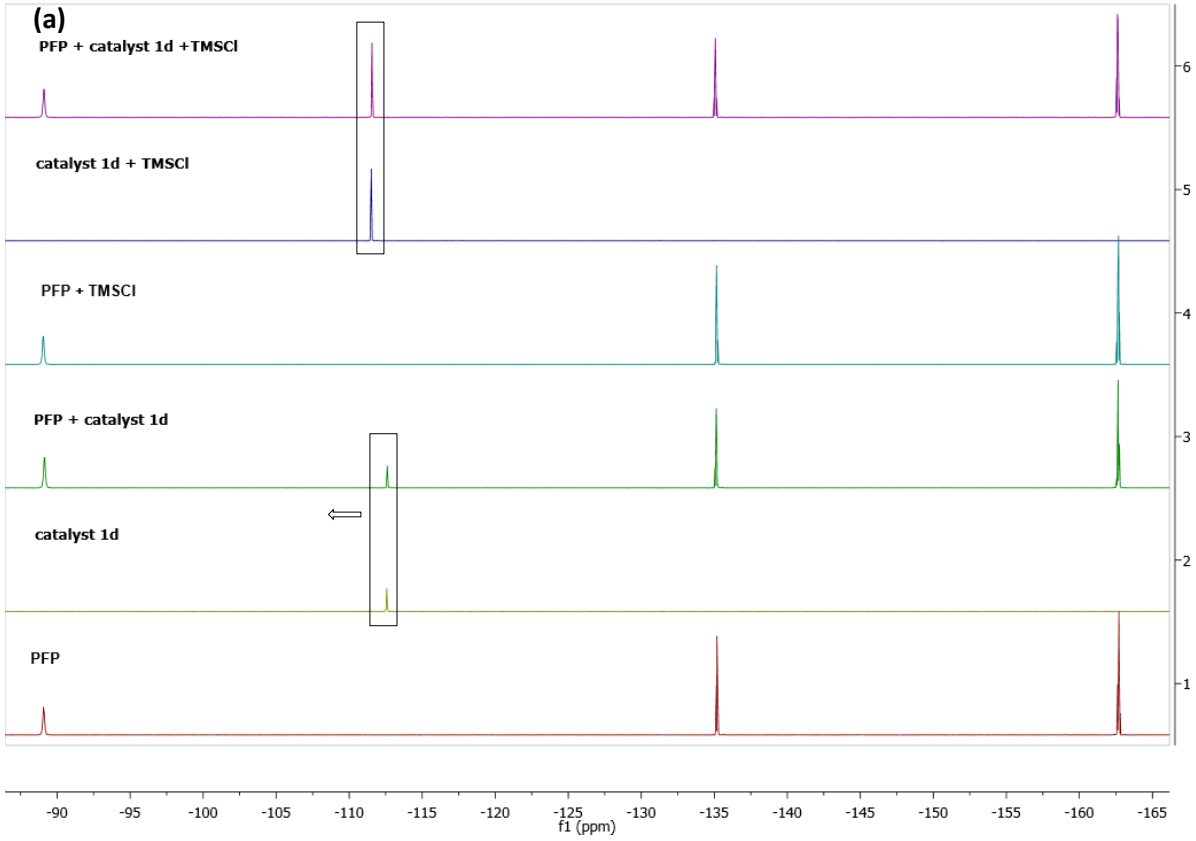
Table 5.10 Catalyst loading experiment

Catalyst loading	Conv % after 2 h	rate (2 h)	Conv % after 4 h	rate (4 h)
0.04	0	0	1	0.25
0.08	2	1	5	1.25
0.16	12	6	24	6
0.32	35	17.5	55	13.75

The observation of a 1:2 complex in the NMR is consistent with a kinetic analysis which indicate a rate law that is 2.3 order with respect to the catalyst. This supports a transition state involving two catalyst molecules, and also explains the necessity of a relatively high catalyst loading. Efforts to design an improved catalyst which can further enhance the catalytic halodefluorination are underway in our lab.

Recall, that the reaction rate depends on the structure of the chlorosilane. Therefore, we decided to investigate the nature of the silane in the reaction. To individuate the effect from each reaction component, we evaluated all possible combinations for ^{19}F and ^{1}H NMR spectral

deviation. Fluorinated catalyst **5.7d** was used along with pentafluoropyridine so that ^{19}F NMR could be used to monitor the changes. A significant (>1 ppm in ^{19}F NMR) and a concentration dependent movement of the catalyst's ^{19}F signal was observed when **5.7d** and TMSCl were mixed, in a 1:1 mol ratio (Fig. 5.3). Meanwhile, analysis of TMS signal in the ^{1}H NMR of the same mixture showed that the methyl signal of the chlorosilane displays an upfield shift (~0.4 ppm in ^{1}H NMR) when compared to TMSCl (Fig. 5.4). Thus, we proposed that upon mixing a pentacoordinate silicate ($Me_3SiCl_2^-$) was formed. Further evidence for this species came from HRMS and ^{1}H-DOSY experiments, both of which confirmed the mass of this anion (see experimental section for spectra). This was also evidenced by the increased solubility of the $BnNBu_3Cl$ salt in THF, which proceeds from partially to completely soluble upon addition of the TMSCl, at room temperature (note, that the catalyst is soluble in THF at 80 ^{o}C even in the absence of TMSCl). It is expected that the formation of $Me_3SiCl_2^-$ upon addition facilitates the reaction in multiple ways. First, as mentioned previously, it is well known that anion-π interactions can be strong and we anticipated that this would be counterproductive. Thus, the quantitative formation of the dichlorosilicate species prevents the formation of the undesired complex. Second, the delivery of the chloride to the perfluoroarene, would simultaneously generate a TMSCl very near where the fluoride will be generated, and may facilitate the fluoride extrusion step.[145]


(a)
PFP + catalyst 1d +TMSCl
catalyst 1d + TMSCl
PFP + TMSCl
PFP + catalyst 1d
catalyst 1d
PFP
6
5
4
3
2
1
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
f1 (ppm)

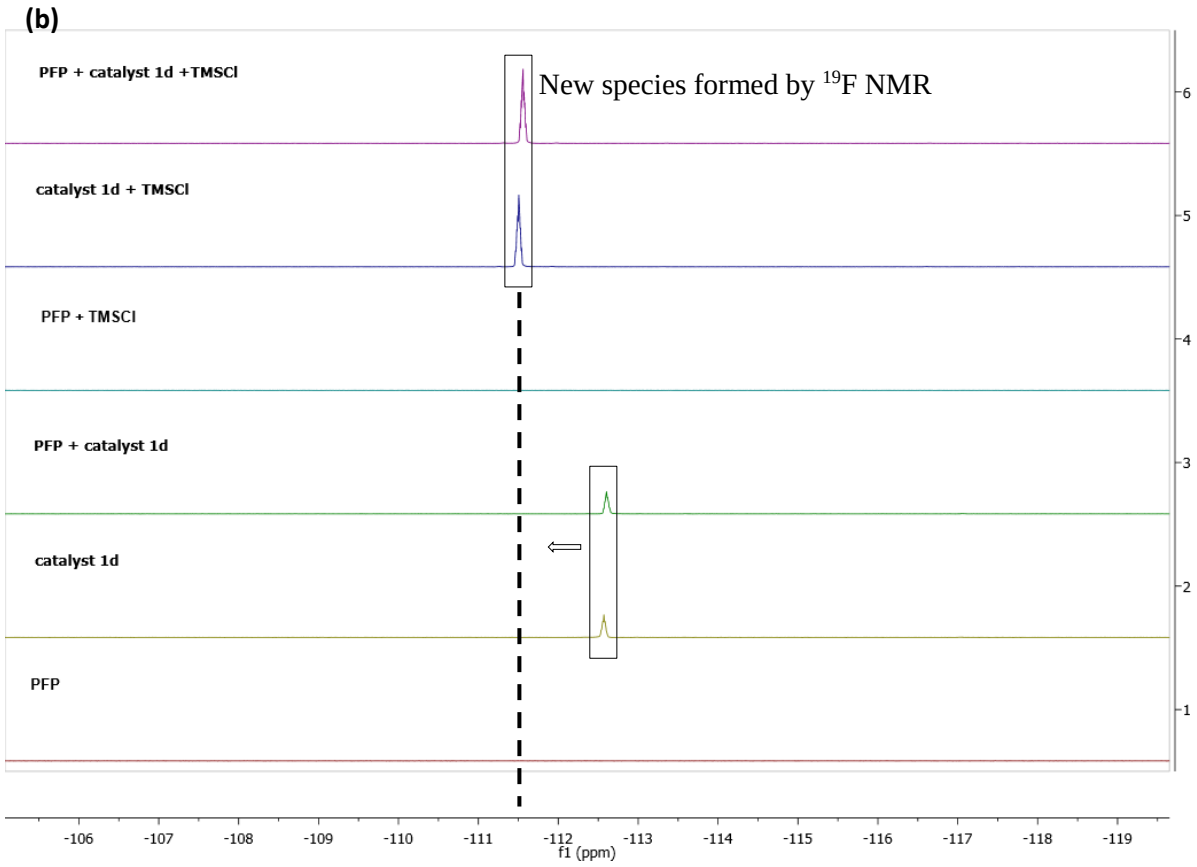


Figure 5.3 (a) ^{19}F NMR spectra for the formation of a new silane species, (b) an expansion of the region of 105-120 ppm of (a)

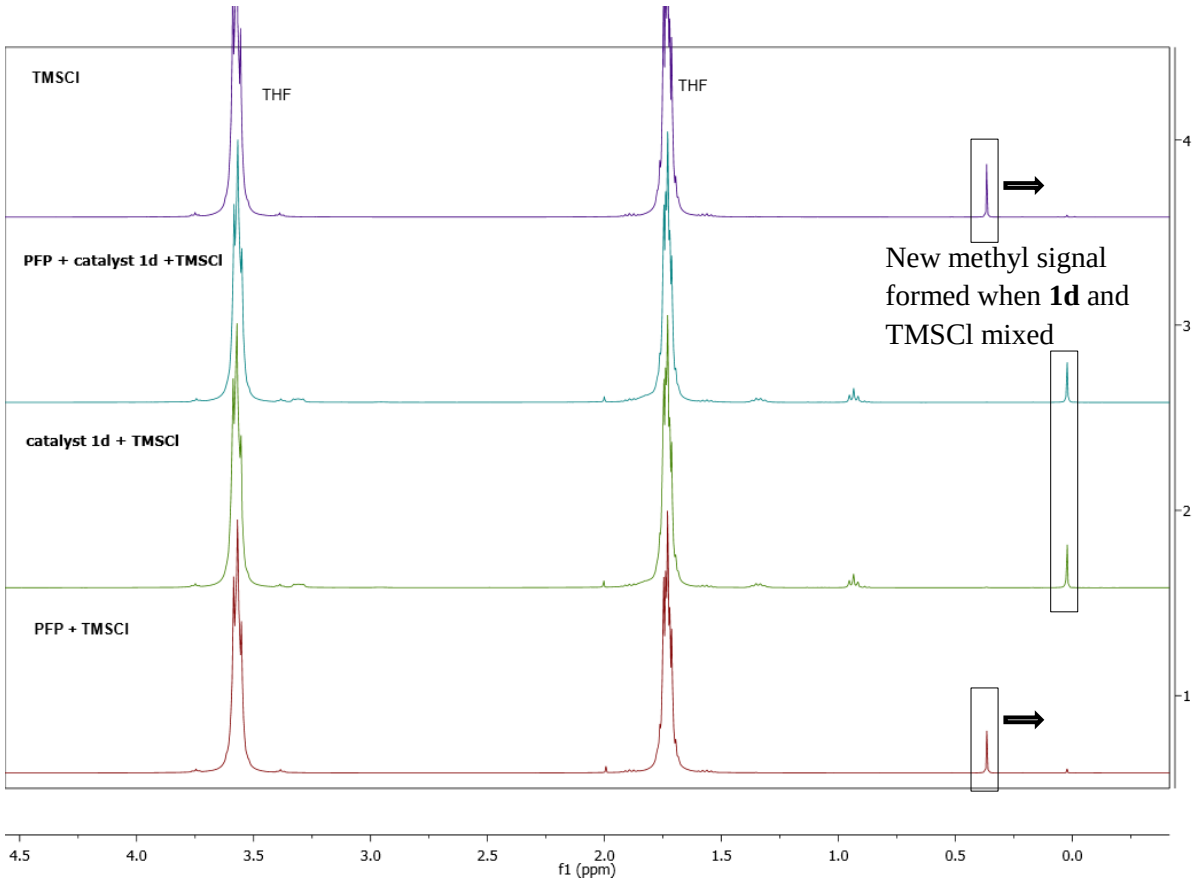


Figure 5.4 Formation of $Me_3SiCl_2^-$ observed by ^1H NMR

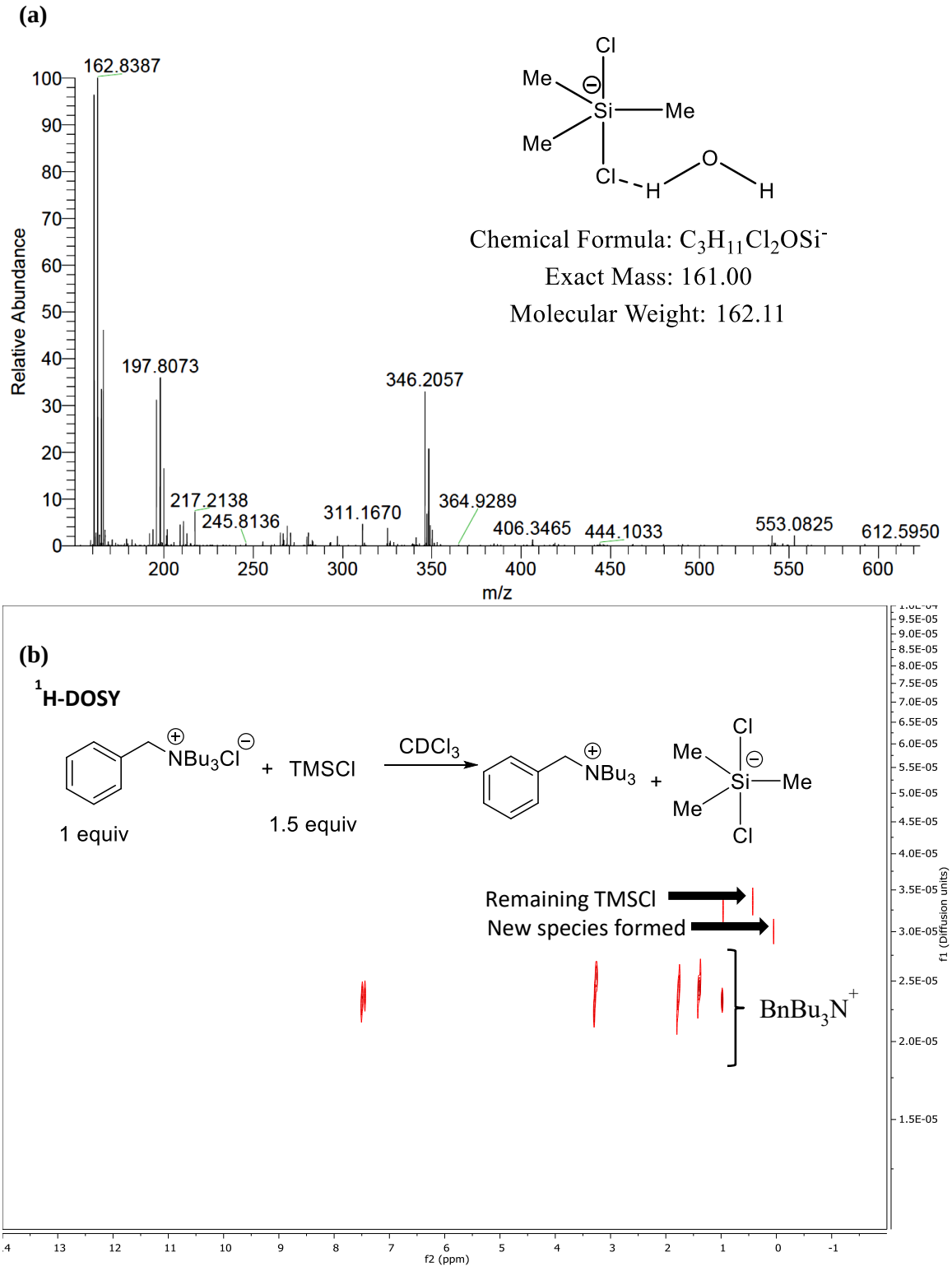
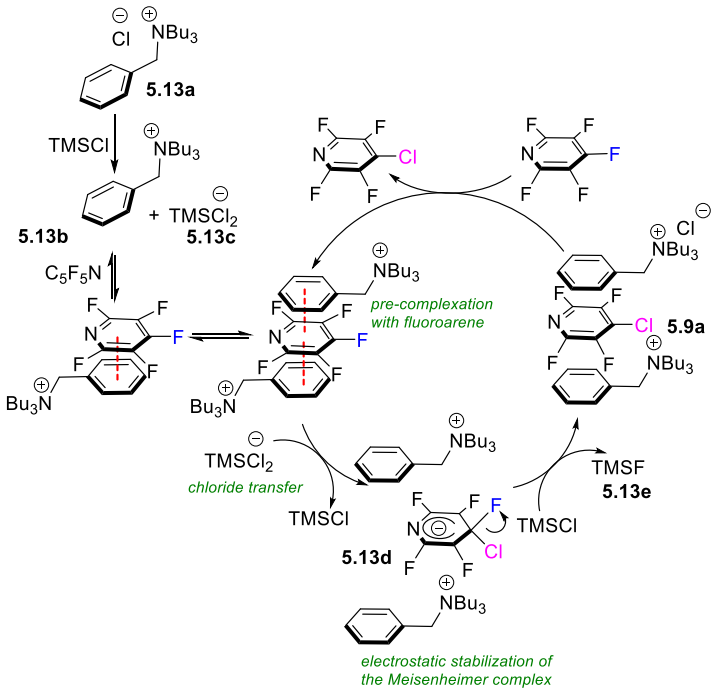


Figure 5.5 (a) $Me_3SiCl_2^-$ observed by HRMS, (b) $Me_3SiCl_2^-$ observed by ^{1}H-DOSY experiment.

Based on the above mechanistic information we propose the following plausible mechanism for the catalytic retro-Halex of perfluoroarenes (Scheme 5.13). First, a chloride transfer from $BnNBu_3Cl$ to TMSCl generates the active chloride source, $Me_3SiCl_2^-$ (**5.13c**). Favorable aromatic donor-acceptor interactions lead to complexation of the fluoroarene with the $BnNBu_3(TMSCl_2)$ catalyst derivative, which bring the catalyst and substrate in close proximity. According to NMR titration experiments the formation of both a 1:1 complex as well as a 2:1 complex ($BnNBu_3(TMSCl_2)$:perfluoroarene) is possible. Initial rate analysis indicates the reaction is greater than second order in catalyst concentration, which is consistent with the necessary high catalyst loading. Preorganization of the catalyst with the perfluoroarenes facilitate the formation of the Meisenheimer complex (**5.13d**) upon chloride transfer from $Me_3SiCl_2^-$. Next, TMSCl assisted extrusion[145] of fluoride generates the chlorofluoroarene (**5.9a**) which is associated with the ammonium cation. The catalytic cycle is completed by displacement of the chlorodefluorinated product (**5.9a**) with another substrate molecule.



Scheme 5.13 Plausible mechanism for the catalytic retro-Halex reaction

5.3 Summary of catalytic retro-Halex reaction

During efforts of develop a selective retro-Halex reaction, we have here demonstrated the first catalytic S_NAr method, which selectively substitutes a C–F bond of perfluoroarenes with a C–Cl bond. Quaternary ammonium chloride salts with bulk on the nitrogen atom facilitate the reaction. Among the catalysts tested, $BnNBu_3Cl$ was determined to be the best chloride transfer catalyst, and importantly provides insights into potential strategies that can facilitate otherwise impossible S_NAr reactions. This reaction is characterized by ground state elevation of the chloride and its conversion to a silicate, transition state preorganization by aromatic donor-acceptor interactions between the substrate and catalyst, attractive electrostatic interactions that stabilize the Meisenheimer intermediate. Finally the use of TMSCl to facilitate the breakdown of the intermediate, and of course make the entire process exergonic. These strategies should be extendable to other types of nucleophiles and thus may have significant impact on future work on S_NAr catalysis. Here, we demonstrated the feasibility of catalyzing the retro-Halex reaction and have shown how it can provide access to new chlorofluoroarenes. Furthermore, we demonstrated how these can immediately be used with more traditional chemistry to access derivatized multifluorinated arenes.

5.4 Experimental section

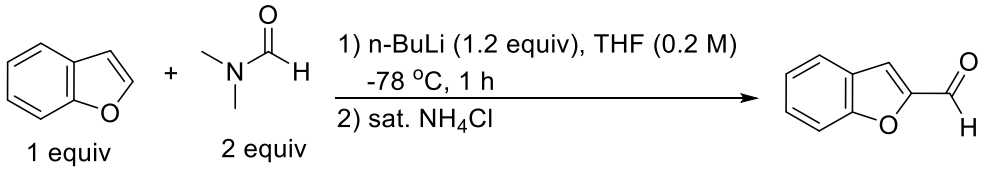
General Experimental

All reagents were obtained from commercial suppliers (Sigma-Aldrich, Oakwood Chemicals, Alfa Aesar, Matrix Scientific, VWR) and used without further purification unless otherwise noted. Acetonitrile (CH_3CN) was dried over molecular sieves and THF was obtained from a solvent purification system. 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]oxazole (Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002), 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]thiazole (Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An,

X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564) were synthesized according to literature procedures. Reactions were monitored by ^{19}F NMR. NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer or a 400 MHz Unity Inova spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual solvent peak while ^{19}F is set relative to an external standard. IR spectra were recorded on a Nicolet iS50 FT-IR. Melting points were determined on a Mel-Temp apparatus and reported uncorrected. Purifications were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica (4 g, 12 g, 24 g, 40 g, or 80 g) with product detection at 254, 280 nm and by ELSD (evaporative light scattering detector). Substrate synthesis reactions were monitored by thin layer chromatography (TLC), obtained from Sorbent Technology Silica XHL TLC Plates, w/UV254, glass backed, 250 μm, and were visualized with ultraviolet light or potassium permanganate.

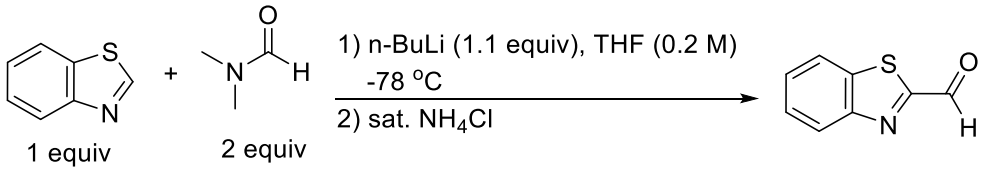
Synthesis of chlorination catalysts

Synthesis of benzofuran-2-carbaldehyde (S1)



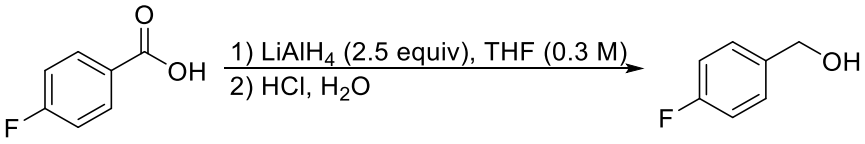
The title compound was synthesized according to a modified literature procedure (Gigant, N.; Claveau, E.; Bouyssou, P.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 844). To a solution of benzofuran (2.5 g, 21.16 mmol) in dry THF (0.2 M) cooled at -78 °C under Ar was added *n*-BuLi (15.9 mL, 1.6 M in hexane, 25.39 mmol), dropwise. After stirring the mixture for 1 h at -78 °C, DMF (3.26 mL, 42.32 mmol) was added dropwise and stirred for another 4.5 h at -78 °C. After the complete consumption of benzofuran, judged by TLC (hexane:DCM 1:1), the reaction was quenched with sat. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and combined organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*. The resultant crude residue was purified by flash chromatography using hexane:EtOAc (0% EtOAc for 5 cv, 0-10% EtOAc for 5-12 cv, 10% EtOAc for 12-18 cv, 10-100% EtOAc for 18-23 cv and and then held at 100% EtOAc for 23-26 cv) on 40 g silica column to afford **benzofuran-2-carbaldehyde** as a yellow solid in 94% yield (3.1 g, 19.9 mmol). The spectral data of the compound matched with the literature (Gigant, N.; Claveau, E.; Bouyssou, P.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 844).

Synthesis of benzo[*d*]thiazole-2-carbaldehyde (S2)



The title compound was synthesized according to a modified literature procedure (Ono, M.; Hayashi, S.; Kimura, H.; Kawashima, H.; Nakayama, M.; Saji, H. *Biorg. Med. Chem.* **2009**, *17*, 7002). To a solution of benzothiazole (2.5 g, 18.5 mmol) in dry THF (0.4 M) cooled at -78 °C under Ar was added *n*-BuLi (12.7 mL, 1.6 M in hexane, 20.3 mmol), dropwise. After stirring the mixture for 1 h at -78 °C, DMF (2.85 mL, 37.0 mmol) was added dropwise and stirred for another 3.5 h at -78 °C. After the complete consumption of benzothiazole, judged by TLC (hexane:DCM 1:1), the reaction was quenched with sat. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and combined organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*. The resultant crude residue was purified by flash chromatography using hexane:EtOAc (0% EtOAc for 5 cv, 0-5% EtOAc for 5-12 cv, 5% EtOAc for 12-35 cv, 5-100% EtOAc for 35-43 cv and then held at 100% EtOAc for 43-47 cv) on 80 g silica column to afford **benzo[*d*]thiazole-2-carbaldehyde** as a yellow solid in 50% yield (1.5 g, 9.2 mmol). The spectral data of the compound matched with the literature (Nagasawa, Y.; Tachikawa, Y.; Yamaguchi, E.; Tada, N.; Miura, T.; Itoh, A. *Adv. Synth. Catal.* **2016**, *358*, 178).

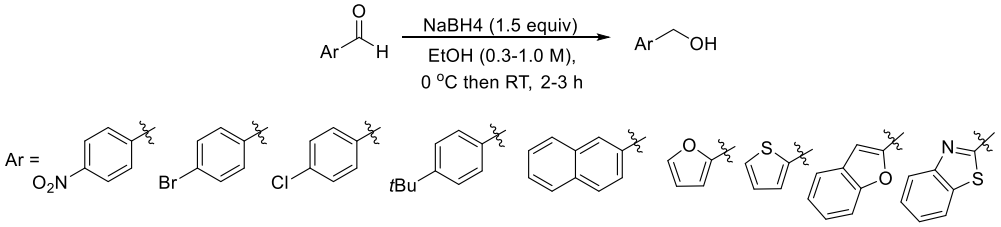
Synthesis of (4-fluorophenyl)methanol (S3)



In a flame dried two-necked round-bottomed flask charged with a stir bar, an ice cold slurry of $LiAlH_4$ (1.35 g, 35.7 mmol) in THF (35 mL) was added a solution of 4-fluorobenzoic acid (2.0 g, 14.3 mmol) in THF (10 mL) under Ar. The mixture was allowed to warm to room temperature and stirred overnight. After the complete consumption of the 4-fluorobenzoic acid (TLC hexane:EtOAc 70:30, buffered with 1% acetic acid), the reaction was cooled down to 0 °C and quenched carefully with 2 M HCl. The mixture was extracted with EtOAc (2x) and combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the

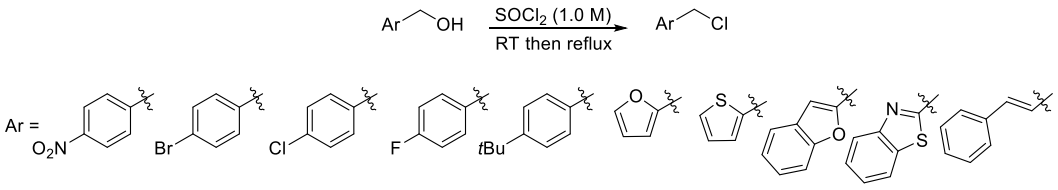
corresponding alcohol product as a light yellow solid in quantitative yield (1.8 g, 14.3 mmol) which was taken to the next step without further purification. The spectral data of the compound matched with the literature (Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993).

General procedure A for the reduction of *para*-substituted benzyl aldehydes



In a flame dried two-necked round-bottomed flask charged with a stir bar $NaBH_4$ (1.5 equiv) was added in a one portion to a solution of the benzyl aldehyde at 0 °C in EtOH under Ar. The mixture was allowed to warm to room temperature and stirred. After the complete consumption of the aldehyde starting material (TLC, hexane:EtOAc 90:10), the reaction was quenched with 10% NaOH and it was stirred for another ~10 min. The crude mixture was rotavaped to remove EtOH. Then the aqueous mixture was extracted with DCM (3x) and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the corresponding alcohol product which was taken to the next step without further purification.

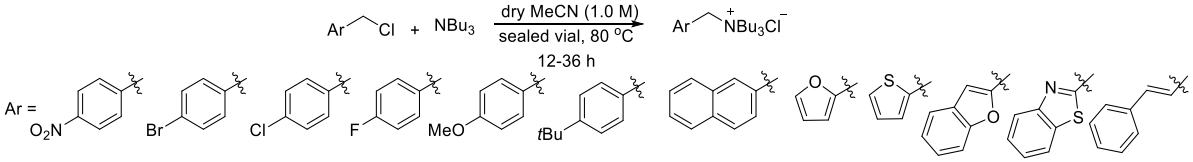
General procedure B for the chlorination of *para*-substituted benzyl alcohols



In a flame dried two-necked round-bottomed flask charged with a stir bar, $SOCl_2$ (1.0 M) was added followed by the corresponding benzyl alcohol. The reaction mixture was stirred at reflux

until the completion of the reaction (TLC, DCM: MeOH 99:1). The crude mixture was rotavaped, and then placed in a vacuum to remove excess $SOCl_2$ to yield the corresponding chloride product which was taken to the next step without further purification.

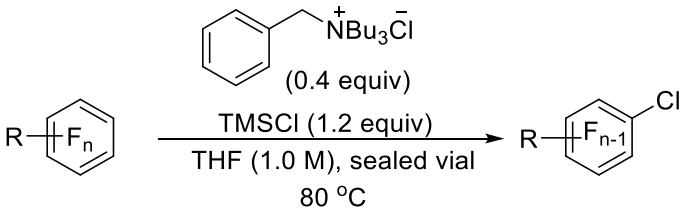
General procedure C for the amine substitution of *para*-substituted benzyl chlorides



A sealed vial was charged with the corresponding benzyl chloride (1.0 equiv), tributylamine (1.2 equiv), MeCN (1.0 M) and the reaction was stirred while heating at 80 °C in an oil bath. Aliquots were taken out and diluted with $CDCl_3$ to monitor the reaction progress (^{1}H NMR). After the complete consumption of starting material, CH_3CN was removed *via* rotavap. The compound was purified *via* trituration. In a 50 mL round-bottomed flask, the sample was dissolved in a minimal amount of DCM and hexane (10x volume of DCM used) was added all at once with vigorous stirring of the mixture, which resulted in the selective dissolution of the excess tributylamine and DCM into the hexane layer, leaving behind the product as a solid. The product was then separated by simple decantation of the hexane layer and washed twice with fresh hexane. Finally, the product was rotavaped and then, placed in a vacuum to remove any residual hexane to yield the title compound.

If further purification was needed, to the triturated solid was added EtOAc (~50 mg salt per mL of EtOAc) and then heated to boil to selectively extract impurities. The mixture was cooled down to rt and the solid product was separated by simple decantation of the EtOAc layer and washed once with fresh EtOAc. Then the product was rotavaped, placed in a vacuum to remove any residual EtOAc.

General procedure D for the catalytic chlorination of perfluoroarenes



A sealable vial was charged with the fluoroarene (1.0 equiv), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (0.4-1.0 equiv), THF (1.0 M), TMSCl (1.2-2.4 equiv) and sealed. The reaction was stirred while heating at 80 °C in an oil bath. Aliquots were taken out and diluted with $CDCl_3$ to monitor the reaction progress by ^{19}F NMR. After the complete consumption of starting material the reaction was allowed to cool to rt. If the product is volatile, the crude reaction was spiked with a known amount of trifluoroacetic acid (TFA) as an internal standard and an NMR yield was obtained. The appropriate workup depends on the volatility of the substrate, *vide infra*.

General workup method E for the isolation of chlorinated polyfluoroarenes (for volatile products).

After reaction completion as judged by ^{19}F NMR, the reaction was cooled to rt. The crude mixture was extracted with pentane (10 mL) and washed with water (10 mL x 2). The water wash removed most of the remaining catalyst (*N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride) and THF partially, leaving the product primarily in pentane layer. The pentane layer contains the desired product, some THF, small amounts of catalyst, and benzyl chloride which arises from catalyst decomposition was rotavaped with no heat to obtain a concentrated mixture. Then, it was transferred to a microwave vial (Biotage Microwave Reaction Kit, 2-5 mL, part # 351521), and water (2 mL) was added and sealed. The mixture was heated at 175 °C for 30 minutes (Biotage Initiator) to decompose benzyl chloride formed during the halogenation reaction. Nucleophilic

scavengers, which may have helped remove the benzylic chloride, were found to attack the product.

The vial was allowed to cool down to rt and pentane (5 mL) was added. Phases were separated and the organic layer was washed with 1M HCl (2 mL x 3) to remove tributylamine formed during the decomposition of remaining catalyst. The organic layer was dried over $MgSO_4$ and passed through a silica plug. The silica plug was eluted with a minimal amount of additional pentane. Eluted pentane layer was rotavaped with no heat to yield the title compound with moderate yields and moderate purities. To determine purity, the isolated product was spiked with a known amount of 1,2,4,5-tetrafluorobenzene as an internal standard. Both ^{19}F NMR and ^{1}H NMR were recorded. Purity was calculated by integrating and comparing proton signals of 1,2,4,5-tetrafluorobenzene with the extra signals (arise mainly from residual solvents and benzyl chloride) in the isolated material.

General method F for the isolation of chlorinated polyfluoroarenes (for relatively nonvolatile products).

After reaction completion (^{19}F NMR), the reaction was cooled to RT. Then the THF was removed *via* rotavap. The residue was treated with deionized water (10 mL) and extracted with DCM (2 x 10 mL). The organic portions were combined and washed with 1M HCl to remove residual tributylamine. Then the DCM layer was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo,* and purified by normal phase chromatography.

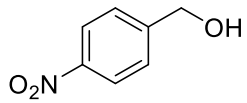
General method G for the isolation of chlorinated polyfluoroarenes (for relatively nonvolatile products).

General method **G** was chosen over General method **F** when the product's water solubility creates problems during the workup. After reaction completion as judged by ^{19}F NMR, the reaction was

cooled down to RT. Then the volatiles were removed *via* rotavap. The residue was purified by normal phase chromatography with no additional workup.

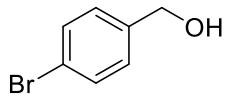
Synthesis of *para*-substituted benzyl alcohols

Synthesis of (4-nitrophenyl)methanol (S-4a)



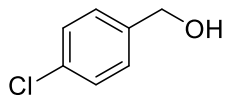
General procedure A was followed using 4-nitrobenzaldehyde (1.5 g, 9.93 mmol), $NaBH_4$ (0.56 g, 14.9 mmol) and EtOH (10 mL) to afford **S-4a** in quantitative yield (1.52 g, 9.93 mmol) as a white solid which was carried to the next step without further purification.

Synthesis of (4-bromophenyl)methanol (S-4b)



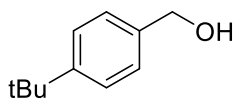
General procedure A was followed using 4-bromobenzaldehyde (1.5 g, 8.10 mmol), $NaBH_4$ (0.46 g, 12.16 mmol) and EtOH (8 mL) to afford **S-4b** in 97% yield (1.47 g, 7.9 mmol) as a white solid which was carried to the next step without further purification.

Synthesis of (4-chlorophenyl)methanol (S-4c)



General procedure A was followed using 4-chlorobenzaldehyde (1.5 g, 10.67 mmol), $NaBH_4$ (0.60 g, 16.0 mmol) and EtOH (10 mL) to afford **S-4c** in 94% yield (1.42 g, 10.0 mmol) as a white solid which was carried to the next step without further purification.

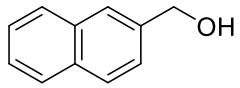
Synthesis of (4-(*tert*-butyl)phenyl)methanol (S-4d)



General procedure A was followed using 4-(*tert*-butyl)benzaldehyde (1.5 g, 9.25 mmol), $NaBH_4$ (0.52 g, 13.88 mmol) and EtOH (9.2 mL) to

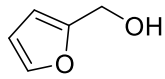
afford **S-4d** in quantitative yield (1.52 g, 9.25 mmol) as a colorless liquid which was carried to the next step without further purification.

Synthesis of naphthalen-2-ylmethanol (S-4f)



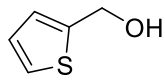
General procedure A was followed using 2-naphthaldehyde (1.0 g, 6.4 mmol), $NaBH_4$ (0.36 g, 9.6 mmol) and EtOH (6.5 mL) to afford **S-4f** in 73% yield (0.74 g, 4.66 mmol) as a white solid which was carried to the next step without further purification.

Synthesis of furan-2-ylmethanol (S-4g)



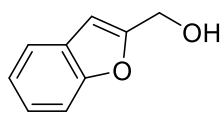
General procedure A was followed using furan-2-carbaldehyde (1.29 mL, 15.61 mmol), $NaBH_4$ (0.88 g, 23.42 mmol) and EtOH (15 mL) to afford **S-4g** in 75% yield (1.15 g, 11.71 mmol) as a colorless oil which was carried to the next step without further purification.

Synthesis of thiophen-2-ylmethanol (S-4h)



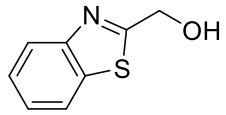
General procedure A was followed using thiophene-2-carbaldehyde (1.67 mL, 17.83 mmol), $NaBH_4$ (1.01 g, 26.74 mmol) and EtOH (17.8 mL) to afford **S-4h** in quantitative yield (2.1 g, 17.83 mmol) as a light yellow liquid which was carried to the next step without further purification.

Synthesis of benzofuran-2-ylmethanol (S-4i)



General procedure A was followed using benzofuran-2-carbaldehyde (1.0 g, 6.84 mmol), $NaBH_4$ (0.39 g, 10.26 mmol) and EtOH (13.7 mL, 0.5 M) to afford **S-4i** in quantitative yield (1.01 g, 6.84 mmol) as a white solid which was carried to the next step without further purification.

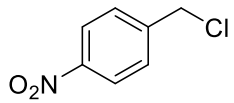
Synthesis of benzo[*d*]thiazol-2-ylmethanol (S-4j)



General procedure A was followed using benzo[*d*]thiazole-2-carbaldehyde (1.0 g, 6.12 mmol), $NaBH_4$ (0.35 g, 9.18 mmol) and EtOH (18 mL, 0.3 M) to afford **S-4j** in 83% yield (0.84 g, 5.08 mmol) as a light yellow solid which was carried to the next step without further purification.

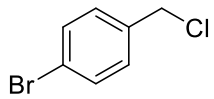
Synthesis of *para*-substituted benzyl chlorides

Synthesis of 1-(chloromethyl)-4-nitrobenzene (S-5a)



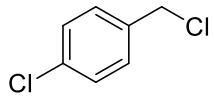
General procedure B was followed using **(4-nitrophenyl)methanol (S-4a)** (0.76 g, 5.0 mmol), $SOCl_2$ (5.0 mL) to afford **S-5a** in 67% yield (0.58 g, 3.4 mmol) as a white solid which was carried to the next step without further purification.

Synthesis of 1-bromo-4-(chloromethyl)benzene (S-5b)



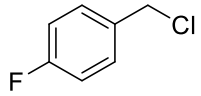
General procedure B was followed using **(4-bromophenyl)methanol (S-4b)** (0.75 g, 4.01 mmol), $SOCl_2$ (4.0 mL) to afford **S-5b** in quantitative yield (0.82 g, 4.0 mmol) as a white solid which was carried to the next step without further purification.

Synthesis of 1-chloro-4-(chloromethyl)benzene (S-5c)



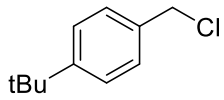
General procedure B was followed using **(4-chlorophenyl)methanol (S-4c)** (0.75 g, 5.26 mmol), $SOCl_2$ (5.3 mL) to afford **S-5c** in quantitative yield (0.84 g, 5.26 mmol) as a white solid which was carried to the next step without further purification.

Synthesis of 1-(chloromethyl)-4-fluorobenzene (S-5d)



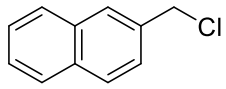
General procedure B was followed using **(4-fluorophenyl)methanol (S2)** (0.70 g, 5.55 mmol), $SOCl_2$ (5.5 mL) to afford **S-5d** in 85% yield (0.68 g, 4.7 mmol) as a brown solid which was carried to the next step without further purification.

Synthesis of 1-(*tert*-butyl)-4-(chloromethyl)benzene (S-5e)



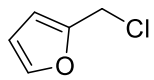
General procedure B was followed using **(4-(*tert*-butyl)phenyl)methanol (S-4d)** (0.75 g, 4.57 mmol), $SOCl_2$ (4.5 mL) to afford **S-5e** in 95% yield (0.79 g, 4.34 mmol) as a colorless oil which was carried to the next step without further purification.

Synthesis of 2-(chloromethyl)naphthalene (S-5g)



S-5g was synthesized according to a literature procedure (Natale, N. R.; Rogers, M. E.; Staples, R.; Triggle, D. J.; Rutledge, A. *J. Med. Chem.* **1999**, *42*, 3087). The spectral data of the compound matched with the above literature.

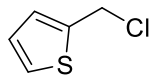
Synthesis of 2-(chloromethyl)furan (S-5h)



S-5h was synthesized according to a modified literature procedure (Duffey, M. O.; England, D. B.; Hu, Z.; Ito, M.; Langston, S. P.; Mcintyre, C.; Mizutani, H.; Xu, H.; Millennium Pharmaceuticals, Inc., USA, **2015**). To a solution of **thiophen-2-ylmethanol (S-4g)** (1.0 g, 8.75 mmol) in DCM (17.5 mL, 0.5 M) cooled at 0 ^oC was added $SOCl_2$ dropwise (0.96 mL, 13.14 mmol). The reaction was stirred at 0 ^oC for 1 h. After the completion of the reaction determined by TLC (DCM: MeOH 99:1) the reaction was quenched by adding water (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3x) and the combined organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo* to yield **S-5h** as a colorless liquid in 63% yield (600 mg, 5.17 mmol) which was taken to the next step without

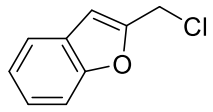
further purification. The spectral data of the compound matched with the literature (Duffey, M. O.; England, D. B.; Hu, Z.; Ito, M.; Langston, S. P.; Mcintyre, C.; Mizutani, H.; Xu, H.; Millennium Pharmaceuticals, Inc., USA, **2015**)

Synthesis of 2-(chloromethyl)thiophene (S-5i)



S-5i was synthesized according to a modified literature procedure (Kumar Muthyala, M.; Choudhary, S.; Pandey, K.; Shelke, G. M.; Jha, M.; Kumar, A. *Eur. J. Org. Chem.* **2014**, *2014*, 2365). To a solution of **furan-2-ylmethanol (S-4h)** (0.80 g, 8.15 mmol) and trimethylamine (1.13 mL, 8.15 mmol) in DCM (8.2 mL, 0.1 M) cooled at 0 ^{o}C was added $SOCl_2$, dropwise (0.78 mL, 10.6 mmol). After stirring the mixture at 0 ^{o}C until the completion of the reaction (determined by TLC, DCM: MeOH 99:1). The reaction was quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3x) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield **S-5i** as a colorless oil in 52% yield (600 mg, 4.55 mmol) which was taken to the next step without further purification. The spectral data of the compound matched with the literature (Davis, M. C. *Synth. Commun.* **2005**, *35*, 2079).

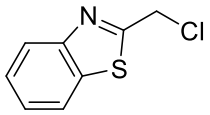
Synthesis of 2-(chloromethyl)benzofuran (S-5j)



S-5j was synthesized according to a modified literature procedure (Ferorelli, S.; Abate, C.; Pedone, M. P.; Colabufo, N. A.; Contino, M.; Perrone, R.; Berardi, F. *Biorg. Med. Chem.* **2011**, *19*, 7612). To a solution of **benzofuran-2-ylmethanol (S-4i)** (0.50 g, 3.37 mmol) in a mixture of DMF (0.7 mL, 4.8 M) and THF (3.8 mL, 1.0 M) at RT was added $SOCl_2$ dropwise (0.37 mL, 5.06 mmol). After stirring the mixture for at 60 ^{o}C until reaction completion (determined by TLC, DCM: MeOH 99:1) the reaction was stirred further at rt for 30 min. Then the volatiles were evaporated *in vacuo* and the crude residue was dissolved in water. The mixture was extracted with EtOAc (3x) and combined organic layer was

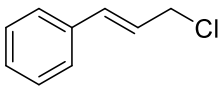
washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield **S-5j** as a white solid in 89% yield (500 mg, 3.01 mmol) which was taken to the next step without further purification. The spectral data of the compound matched with the literature (Ferorelli, S.; Abate, C.; Pedone, M. P.; Colabufo, N. A.; Contino, M.; Perrone, R.; Berardi, F. *Biorg. Med. Chem.* **2011**, *19*, 7612).

Synthesis of 2-(chloromethyl)benzo[*d*]thiazole (S-5k)



S-5k was synthesized according to a modified literature procedure (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021). A solution of **benzo[*d*]thiazol-2-ylmethanol (S-4j)** (0.5 g, 3.02 mmol) in CCl_4 (5.0 mL, 0.6 M) and benzene (6.0 mL, 0.5 M) at rt was added to triphenylphosphine (1.2 g, 4.54 mmol) and the mixture was refluxed with stirring. The reaction progress was monitored by TLC (hexane:EtOAc 9:1). After cooling to rt and filtration through celite, the solvent was evaporated *in vacuo*. The resultant crude residue was purified by flash chromatography using hexane:EtOAc (0% EtOAc for 3 cv, 0-10% EtOAc for 3-10 cv, 10% EtOAc for 10-15 cv and then ramped up to 100% EtOAc for 15-20 cv and then held at 100% EtOAc for 20-30 cv) on 24 g silica column to afford **2-(chloromethyl)benzo[*d*]thiazole** in 91% yield (0.55 g, 2.75 mmol) as a yellow solid. The spectral data of the compound matched with the literature (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021).

Synthesis of (3-chloroprop-1-en-1-yl)benzene (S-5l)

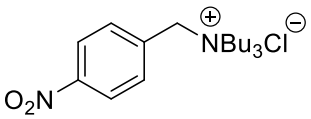


S-5l was synthesized according to a modified literature procedure (Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778). A flame dried round-bottomed flask equipped with a magnetic stir bar was charged with DCM (45 mL, 0.5 M) and 3-phenylprop-2-en-1-ol (3.0 g, 22.35 mmol) under argon. The solution

was cooled to 0 °C and $SOCl_2$ (16.3 mL, 223.5 mmol) was added dropwise. The reaction was stirred at 0 °C while the progress was monitored by TLC (hexane:EtOAc 9:1). After 2.5 h, the reaction was stopped and allowed to warm to rt slowly. It was quenched with ice water, extracted with DCM (3x) and washed with sat. $NaHCO_3$. The DCM layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant crude residue was purified by flash chromatography using hexane:DCM (0-2% DCM for 0-22 cv, 2-15% DCM for 22-27 cv, 15% DCM for 27-36, 15-100% DCM for 36-46 cv and then held at 100% DCM for 46-52 cv) on 80 g silica column to afford a colorless liquid **(3-chloroprop-1-en-1-yl)benzene** in 25% yield (0.85 g, 5.58 mmol). The spectral data of the compound matched with the literature (Wang, J.; Tong, X.; Xie, X.; Zhang, Z. *Org. Lett.* **2010**, *12*, 5370).

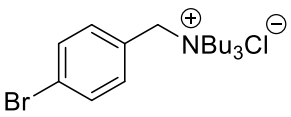
Synthesis of quaternary ammonium chloride salts

Synthesis of *N*,*N*-dibutyl-*N*-(4-nitrobenzyl)butan-1-aminium chloride (5.7a)



General procedure C was followed using **1-(chloromethyl)-4-nitrobenzene (S-5a)** (0.30 g, 1.74 mmol), tributylamine (0.5 mL, 2.09 mmol) in MeCN (1.8 mL) to afford **5.7a** in 87% yield (0.54 g, 1.51 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.19 (d, J = 8.6 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 5.47 (s, 2H), 3.43 – 3.27 (m, 6H), 1.79 (p, J = 8.1 Hz, 6H), 1.37 (h, J = 7.4 Hz, 6H), 0.97 (t, J = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 148.9, 135.3, 134.6, 123.8, 62.1, 59.5, 24.7, 19.9, 13.7. FT-IR cm^{-1} 3387, 2961, 1523, 1348. HRMS (ESI) calcd, $C_{19}H_{33}N_2O_2^+$ 321.2537; observed, 321.2520. mp 192-193 °C.

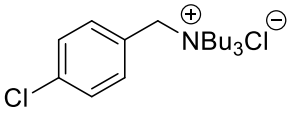
Synthesis of *N*-(4-bromobenzyl)-*N*,*N*-dibutylbutan-1-aminium chloride (5.7b)



General procedure C was followed using **1-bromo-4-(chloromethyl)benzene (S-5b)** (0.62 g, 3.02 mmol), tributylamine (0.8 mL, 3.31 mmol) in MeCN (3.0 mL) to afford **5.7b** in 90% yield (1.06 g, 2.72 mmol) as a

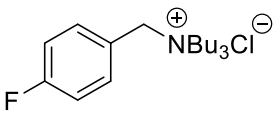
white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (s, 4H), 5.12 (s, 2H), 3.32 (dd, *J* = 11.8, 5.2 Hz, 6H), 1.75 (dd, *J* = 15.3, 7.4 Hz, 6H), 1.39 (h, *J* = 7.4 Hz, 6H), 0.98 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 134.6, 132.4, 126.9, 125.3, 62.6, 58.9, 24.6, 19.9, 13.7. FT-IR cm^{-1} 3390, 2963, 737. HRMS (ESI) calcd, $C_{19}H_{33}BrN^{+}$ 354.1791; observed, 354.1788. mp 165-166 °C.

Synthesis of *N*,*N*-dibutyl-*N*-(4-chlorobenzyl)butan-1-aminium chloride (5.7c)



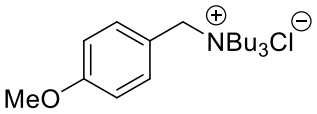
General procedure C was followed using **1-chloro-4-(chloromethyl)benzene (S-5c)** (0.40 g, 2.48 mmol), tributylamine (0.65 mL, 2.73 mmol) in MeCN (2.5 mL) to afford **5.7c** in 86% yield (0.74 g, 2.13 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.13 (s, 2H), 3.36 – 3.27 (m, 6H), 1.76 (p, *J* = 8.1 Hz, 6H), 1.38 (h, *J* = 7.4 Hz, 6H), 0.97 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.8, 134.2, 129.3, 126.4, 62.5, 58.8, 24.5, 19.8, 13.6. FT-IR cm^{-1} 3393, 2959. HRMS (ESI) calcd, $C_{19}H_{33}ClN^{+}$ 310.2296; observed, 310.2280. mp 165-166 °C.

Synthesis of *N*,*N*-dibutyl-*N*-(4-fluorobenzyl)butan-1-aminium chloride (5.7d)



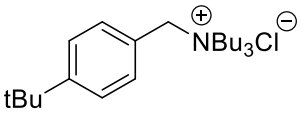
General procedure C was followed using **1-(chloromethyl)-4-fluorobenzene (S-5d)** (0.25 g, 1.73 mmol), tributylamine (0.49 mL, 2.08 mmol) in MeCN (1.73 mL) to afford **5.7d** in 95% yield (0.54 g, 1.64 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -108.9 (ddd, *J* = 13.4, 8.5, 5.1 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (dd, *J* = 8.4, 5.1 Hz, 2H), 7.11 (t, *J* = 8.3 Hz, 2H), 5.10 (s, 2H), 3.41 – 3.18 (m, 6H), 1.75 (p, *J* = 8.0 Hz, 6H), 1.39 (h, *J* = 7.5 Hz, 6H), 0.98 (t, *J* = 7.2 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.7 (d, *J* = 251.9 Hz), 134.8 (d, *J* = 8.5 Hz), 123.7 (d, *J* = 3.4 Hz), 116.2 (d, *J* = 21.6 Hz), 62.4, 58.6, 24.4, 19.7, 13.5. FT-IR cm^{-1} 3388, 2962, 1512, 1227, HRMS (ESI) calcd, $C_{19}H_{33}FN^{+}$ 294.2592; observed, 294.2570. mp 157-159 °C.

Synthesis of *N*,*N*-dibutyl-*N*-(4-methoxybenzyl)butan-1-aminium chloride (5.7e)



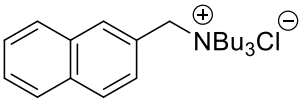
General procedure C was followed using **1-(chloromethyl)-4-methoxybenzene** (0.34 mL, 2.5 mmol), tributylamine (0.59 mL, 2.5 mmol) in MeCN (2.5 mL) to afford **5.7e** in 88% yield (0.75 g, 2.2 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 4.86 (s, 2H), 3.81 (s, 3H), 3.33 – 3.24 (m, 6H), 1.75 (p, *J* = 8.0 Hz, 6H), 1.40 (h, *J* = 7.4 Hz, 6H), 0.98 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.1, 133.9, 119.1, 114.5, 62.7, 58.2, 55.3, 24.3, 19.7, 13.6. HRMS (ESI) calcd, $C_{19}H_{33}FN^{+}$ 294.2592; observed, 294.2570. FT-IR cm^{-1} 3381, 2958, 1514, 1221. HRMS (ESI) calcd, $C_{20}H_{36}NO^{+}$ 306.2791; observed, 301.2777. mp 97-100 ^{o}C.

Synthesis of *N*,*N*-dibutyl-*N*-(4-(*tert*-butyl)benzyl)butan-1-aminium chloride (5.7f)



General procedure C was followed using **1-(*tert*-butyl)-4-(chloromethyl)benzene (S-5e)** (0.40 g, 2.18 mmol), tributylamine (0.57 mL, 2.41 mmol) in MeCN (2.2 mL) to afford **5.7f** in 87% yield (0.70 g, 1.9 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (s, 4H), 4.85 (s, 2H), 3.39 – 3.28 (m, 6H), 1.77 (p, *J* = 8.0 Hz, 6H), 1.43 (h, *J* = 7.3 Hz, 6H), 1.31 (s, 9H), 1.00 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.2, 132.3, 126.3, 124.3, 62.9, 58.4, 34.9, 31.2, 24.5, 19.8, 13.8. FT-IR cm^{-1} 3390, 2960. HRMS (ESI) calcd, $C_{23}H_{42}N^{+}$ 332.3312; observed, 332.3295. mp 195-197 ^{o}C.

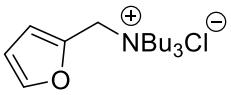
Synthesis of *N*,*N*-dibutyl-*N*-(naphthalen-2-ylmethyl)butan-1-aminium chloride (5.7h)



General procedure C was followed using **2-(chloromethyl)naphthalene (S-5g)** (0.30 g, 1.69 mmol), tributylamine (0.49 mL, 2.04 mmol) in MeCN (1.7 mL) to afford **5.7h** in 92% yield (0.56 g, 1.55 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.84 (dd, *J* = 10.7,

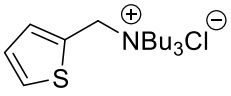
7.8 Hz, 3H), 7.61 – 7.50 (m, 3H), 5.19 (s, 2H), 3.42 – 3.32 (m, 6H), 1.82 (p, *J* = 8.0 Hz, 6H), 1.42 (h, *J* = 7.3 Hz, 6H), 0.98 (t, *J* = 7.4 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.7, 133.2, 132.8, 129.0, 128.5, 128.3, 127.7, 127.6, 127.0, 124.8, 63.3, 58.6, 24.5, 19.8, 13.6. FT-IR cm^{-1} 3391, 2959, 1484. HRMS (ESI) calcd, $C_{23}H_{36}N^+$ 326.2842; observed, 326.2826. mp 145-147 °C.

Synthesis of *N*,*N*-dibutyl-*N*-(furan-2-ylmethyl)butan-1-aminium chloride (5.7i)



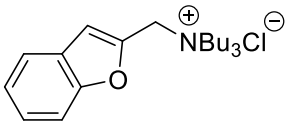
General procedure C was followed using **2-(chloromethyl)furan (S-5h)** (0.30 g, 2.57 mmol), tributylamine (0.73 mL, 3.08 mmol) in MeCN (2.6 mL) to afford **5.7i** in 91% yield (0.70 g, 2.34 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 3.3 Hz, 1H), 6.45 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.06 (s, 2H), 3.36 – 3.26 (m, 6H), 1.76 (dq, *J* = 12.0, 7.8 Hz, 6H), 1.41 (h, *J* = 7.3 Hz, 6H), 0.98 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 144.78, 142.13, 116.66, 111.18, 58.55, 54.85, 23.79, 19.38, 13.27. FT-IR cm^{-1} 3392, 2959. HRMS (ESI) calcd, $C_{17}H_{32}NO^+$ 266.2478; observed, 266.2456. mp 124-125 °C.

Synthesis of *N*,*N*-dibutyl-*N*-(thiophen-2-ylmethyl)butan-1-aminium chloride (5.7j)



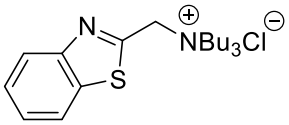
General procedure C was followed using **2-(chloromethyl)thiophene (S-5i)** (0.30 g, 2.26 mmol), tributylamine (0.65 mL, 2.71 mmol) in MeCN (2.3 mL) to afford **5.7j** in 90% yield (0.65 g, 2.03 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 3.3 Hz, 1H), 7.49 (d, *J* = 5.1 Hz, 1H), 7.10 (dd, *J* = 5.2, 3.5 Hz, 1H), 5.22 (s, 2H), 3.41 – 3.29 (m, 6H), 1.81 (p, *J* = 8.1 Hz, 6H), 1.44 (h, *J* = 7.4 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 134.1, 129.4, 127.5, 127.3, 57.9, 56.4, 23.9, 19.3, 13.3. FT-IR cm^{-1} 3393, 2957. HRMS (ESI) calcd, $C_{17}H_{32}NS^+$ 282.2250; observed, 282.2230. mp 152-155 °C.

Synthesis of *N*-(benzofuran-2-ylmethyl)-*N,N*-dibutylbutan-1-aminium chloride (5.7k)



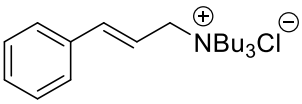
General procedure C was followed using **2-(chloromethyl)benzofuran (S-5j)** (0.25 g, 1.34 mmol), tributylamine (0.30 mL, 1.61 mmol) in MeCN (1.4 mL) to afford **5.7k** in 89% yield (0.44 g, 1.19 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.53 (s, 1H), 7.46 – 7.26 (m, 3H), 5.37 (s, 2H), 3.48 – 3.21 (m, 6H), 1.85 (p, *J* = 7.5 Hz, 6H), 1.45 (h, *J* = 7.4 Hz, 6H), 1.01 (t, *J* = 7.5 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.4, 144.8, 127.0, 126.2, 123.7, 122.2, 114.4, 111.3, 59.5, 56.1, 24.3, 19.8, 13.6. FT-IR cm^{-1} 3461, 2960. HRMS (ESI) calcd, $C_{21}H_{34}NO^{+}$ 316.2635; observed, 316.2619. mp 142-145 °C.

Synthesis of *N*-(benzo[*d*]thiazol-2-ylmethyl)-*N,N*-dibutylbutan-1-aminium chloride (5.7l)



General procedure C was followed using **2-(chloromethyl)benzo[*d*]thiazole (S-5k)** (0.25 g, 1.50 mmol), tributylamine (0.43 mL, 1.81 mmol) in MeCN (1.5 mL) to afford **5.7l** in 87% yield (0.46 g, 1.19 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.90 (m, 1H), 7.57 – 7.45 (m, 2H), 5.57 (s, 2H), 3.59 – 3.49 (m, 6H), 1.87 (p, *J* = 7.8 Hz, 6H), 1.43 (h, *J* = 7.5 Hz, 6H), 0.99 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.6, 152.5, 135.2, 126.6, 126.4, 123.5, 121.6, 59.3, 57.1, 23.9, 19.4, 13.3. FT-IR cm^{-1} 3458, 2957. HRMS (ESI) calcd, $C_{20}H_{33}N_2S^{+}$ 333.2359; observed, 333.2342. mp 102-104 °C.

Synthesis of *N,N*-dibutyl-*N*-cinnamylbutan-1-aminium chloride (5.7m)

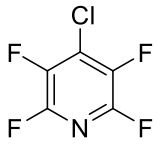


General procedure C was followed using **(3-chloroprop-1-en-1-yl)benzene (S-5l)** (0.5 g, 3.28 mmol), tributylamine (0.94 mL, 3.93 mmol) in MeCN (3.3 mL) to afford **5.7m** in 96% yield (1.06 g, 3.15 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.36 (dtd, *J* = 6.8, 5.2, 4.8, 2.0 Hz, 3H), 7.07 (d, *J* = 15.5 Hz, 1H), 6.17 (dt, *J* = 15.4, 7.6 Hz, 1H), 4.54 (d, *J* = 7.6 Hz, 2H), 3.43

– 3.33 (m, 6H), 1.79 (p, *J* = 15.6, 7.7 Hz, 6H), 1.45 (h, *J* = 7.4 Hz, 6H), 1.01 (t, *J* = 7.4 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 142.9, 134.7, 129.3, 128.8, 127.1, 114.1, 61.6, 58.7, 24.2, 19.7, 13.6. FT-IR cm^{-1} 3378, 2958, 1649. HRMS (ESI) calcd, $C_{21}H_{36}N^+$ 302.2842; observed, 302.2826. mp 145-147 °C.

Catalytic chlorination of perfluoroarenes

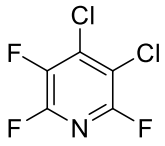
Synthesis of 4-chloro-2,3,5,6-tetrafluoropyridine (5.9a)



General procedure D was followed using pentafluoropyridine (110 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (124.8 mg, 0.4 mmol), TMSCl (152 µL, 1.2 mmol) and THF (1.0 mL) was used to afford **5.9a** in quantitative yield by ^{19}F NMR after adding trifluoroacetic acid (19.2 µL, 0.25 mmol).

Due to the volatility of the product, **General workup method E** was followed to isolate **5.9a** in 35% yield (64.9 mg) and >95% purity as a colorless liquid. For the determination of purity the isolated material (10.0 µL, 16.6 mg) was diluted with $CDCl_3$ (0.35 mL) in an NMR tube and it was spiked with 1,2,4,5-tetrafluorobenzene (5.0 µL, 0.045 mmol). The spectral data of the compound matched with the literature (Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR Spectroscopy of the Non-Metallic Elements*; John Wiley and Sons,Inc., **1997**). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.4 (dt, *J* = 28.1, 14.7 Hz, 2F), -141.3 – -141.7 (m, 2F). FT-IR cm^{-1} 1466, 1238, 952. GC/MS (*m/z*, relative intensity) 187 (M+2, 10), 185 (M+, 30).

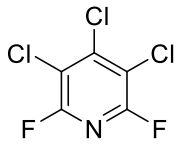
Synthesis of 3,4-dichloro-2,5,6-trifluoropyridine (5.9b)



General procedure D was followed using 3-chloro-2,4,5,6-tetrafluoropyridine (115.2 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (124.8 mg, 0.4 mmol), TMSCl (126.9 µL, 1.0 mmol) and THF (1.0 mL) was used to afford **2b** in 90% yield by ^{19}F NMR after adding trifluoroacetic acid (9.6 µL, 0.125 mmol).

Due to the volatility of the product, **General workup method E** was followed to isolate **5.9b** in 72% yield (145 mg) and 92% purity. For the determination of purity the isolated material (10.0 µL, 16.1 mg) was diluted with $CDCl_3$ (0.35 mL) in an NMR tube and it was spiked with 1,2,4,5-tetrafluorobenzene (5.0 µL, 0.045 mmol). The spectral data of the compound matched with the literature (Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR Spectroscopy of the Non-Metallic Elements*; John Wiley and Sons,Inc., **1997**). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.5 (dd, *J* = 26.1, 13.2 Hz, 1F), -86.5 (dd, *J* = 20.3, 13.2 Hz, 1F), -140.2 (dd, *J* = 26.3, 20.5 Hz, 1F). FT-IR cm^{-1} 1449, 1210, 732. GC/MS (*m/z*, relative intensity) 203 (M+2, 66), 201 (M+, 100).

Synthesis of 3,4,5-trichloro-2,6-difluoropyridine (5.9c)



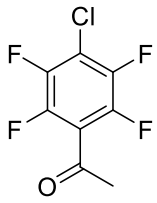
General procedure D was followed using 3,5-dichloro-2,4,6-trifluoropyridine (124.5 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (311.93 mg, 1.0 mmol), TMSCl (253 µL, 2.0 mmol) and THF (1.0 mL) was used to afford **2c** in quantitative yield by ^{19}F NMR after adding trifluoroacetic acid (9.6 µL, 0.125 mmol).

General isolation method G was followed to isolate **5.9c**. The crude material was purified by flash chromatography using hexane:DCM (0% DCM for 0-17 cv, 0-100% DCM for 17-25 cv and then held at 100% DCM for 25-27 cv) on a 40 g silica column to afford **2c** in 63% yield (138 mg) and 72% purity as a colorless liquid. Due to semi-volatile nature of compound **2c** limited effort was made to to remove residual solvents.

For the determination of purity the isolated material (10.0 µL, 15.2 mg) was diluted with $CDCl_3$ (0.35 mL) in an NMR tube and it was spiked with 1,2,4,5-tetrafluorobenzene (5.0 µL, 0.045 mmol). The spectral data of the compound matched with the literature (Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR Spectroscopy of the Non-Metallic Elements*; John Wiley and Sons,Inc.,

1997). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -68.4 (2F). FT-IR cm^{-1} 1393, 1225, 729. GC/MS (*m/z*, relative intensity) 220 (M+2, 100), 218 (M+, 100).

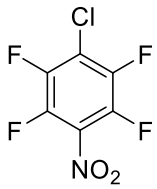
Synthesis of 1-(4-chloro-2,3,5,6-tetrafluorophenyl)ethan-1-one (5.9d)



General procedure D was followed using 1-(perfluorophenyl)ethan-1-one (71.2 µL, 0.5 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (77.9 mg, 0.25 mmol), TMSCl (126.9 µL, 1.0 mmol) and THF (0.5 mL) was used to afford **2d** in 76% yield by ^{19}F NMR after adding trifluoroacetic acid (9.6 µL, 0.125 mmol).

General isolation method G was followed to isolate **5.9d**. The crude material was purified by flash chromatography using hexane:DCM (0% DCM for 0-4 cv, 0-25% DCM for 4-22 cv, 25% DCM for 22-32, 25-100% DCM for 32-35 cv and then held at 100% DCM for 35-37 cv) on a 40 g silica column to afford **2d** in 60% yield (67 mg) as a colorless liquid. Due to volatility of compound **2d** limited effort was made to remove residual solvents. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.1 – -139.2 (m, 2F), -140.6 – -140.8 (m, 2F). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.63 (t, J = 1.8 Hz, 3H). FT-IR cm^{-1} 1714, 1477, 1289. GC/MS (*m/z*, relative intensity) 228 (M+2, 4), 226 (M+, 12).

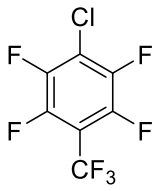
Synthesis of 1-chloro-2,3,5,6-tetrafluoro-4-nitrobenzene (5.9e)



General procedure D was followed using 1,2,3,4,5-pentafluoro-6-nitrobenzene (128.7 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (124.8 mg, 0.4 mmol), TMSCl (152 µL, 1.2 mmol) and THF (1.0 mL) was used.

General isolation method G was followed to isolate **5.9e**. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0-17 cv, 0-100% EtOAc for 17-19 cv and then held at 100% EtOAc for 19-21 cv) on a 40 g silica column to afford **2e** in 80% yield (183 mg, 0.80 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -136.2 – -136.3 (m), -136.3 (q, *J* = 12.6 Hz, 2F), -145.4 – -145.6 (m, 2F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.0 – 143.0 (m), 142.2 – 139.2 (m), 128.9 – 128.4 (m), 117.8 (t, *J* = 18.7 Hz). FT-IR cm^{-1} 1492, 1352, 998, 759. GC/MS (*m/z*, relative intensity) 231 (M+2, 13), 225 (M+, 40). mp 40-42 °C.

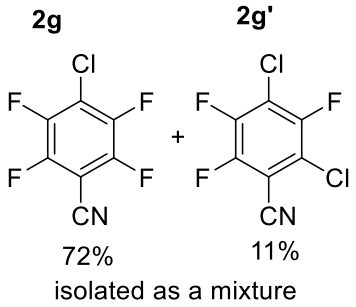
Synthesis of 1-chloro-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (5.9f)



General procedure D was followed using 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)benzene (70.85 µL, 0.5 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (77.9 mg, 0.25 mmol), TMSCl (126.9 µL, 1.0 mmol) and THF (0.5 mL) was used to afford **5.9f** in 90% yield by ^{19}F NMR after adding trifluoroacetic acid (19.1 µL, 0.25 mmol).

Due to the volatility of the product, **General workup method E** was followed to isolate **5.9f** in 30% yield (37 mg) as a colorless liquid. Due to volatility of compound **2f** limited effort was made to remove residual solvents. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -56.2 (t, *J* = 21.9 Hz, 3F), -137.9 – -138.1 (m, 2F), -139.2 – -139.4 (m, 2F). FT-IR cm^{-1} 1483, 1145, 712. GC/MS (*m/z*, relative intensity) 254 (M+2, 35), 252 (M+, 100).

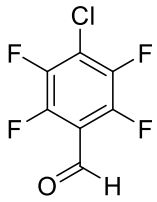
Synthesis of 4-chloro-2,3,5,6-tetrafluorobenzonitrile (5.9g) and 2,4-dichloro-3,5,6-trifluorobenzonitrile (5.9g')



General procedure D was followed using 2,3,4,5,6-pentafluorobenzonitrile (126 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (124.8 mg, 0.4 mmol), TMSCl (152 µL, 1.2 mmol) and THF (1.0 mL) was used.

General isolation method G was followed to isolate **5.9g**. The crude material was purified by flash chromatography using hexane:DCM (0% DCM for 0-15 cv, 0-20% DCM for 15-27 cv, 20% DCM for 27-32, 20-100% DCM for 32-35 cv and then held at 100% DCM for 35-37 cv) on a 40 g silica column to afford **5.9g** in 72% yield and **5.9g'** in 11% yield as a mixture (175 mg combined) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.0 (d, *J* = 11.3 Hz, 1F, minor), -129.7 (dd, *J* = 20.7, 11.3 Hz, 1F, minor), -131.5 – -131.6 (m, 2F, major), -131.7 (d, *J* = 20.8 Hz, 1F, minor), -136.7 – -136.9 (m, 2F, major). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.4 (dt, *J* = 263.7, 15.6, 4.3 Hz), 145.9 – 142.9 (m), 119.8 (tt, *J* = 18.7, 2.6 Hz), 106.9 (t, *J* = 3.6 Hz), 93.2 (t, *J* = 17.3 Hz). Minor product's (**5.9g'**) peaks are labelled on the spectrum. FT-IR cm^{-1} 2249, 1470, 860. GC/MS (*m/z*, relative intensity) **5.9g** 211 (M+2, 33), 209 (M+, 100) and **5.9g'** 227 (M+2, 66), 225 (M+, 100). mp (mixture) 64-66 ^{o}C.

Synthesis of 4-chloro-2,3,5,6-tetrafluorobenzaldehyde (5.9h)

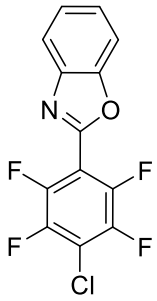


General procedure D was followed using 2,3,4,5,6-pentafluorobenzaldehyde (123.5 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (124.8 mg, 0.40 mmol), TMSCl (126.9 µL, 1.0 mmol) and THF (1.0 mL) was used.

General isolation method G was followed to isolate **5.9h**. The crude material was purified by flash chromatography using hexane:DCM (0% DCM for 1-12 cv, 0-5% DCM for 12-22 cv, 5% DCM for 22-28, 5-100% DCM for 28-35 cv and then held at 100% DCM for 35-37 cv) on a 40 g

silica column to afford **5.9h** in 71% yield (150 mg) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -138.0 – -138.1 (m, 2F), -140.7 – -140.8 (m, 2F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.5 – 176.3 (m), 144.7 (ddt, *J* = 258.7, 14.5, 5.1 Hz), 145.8 – 143.0 (m), 118.1 – 117.6 (m), 117.1 (t, *J* = 14.6 Hz). FT-IR cm^{-1} 1695, 1479, 975. GC/MS (*m/z*, relative intensity) 213 (M+2, 33), 211 (M+, 100). mp 139-141 °C.

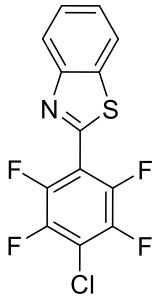
Synthesis of 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]oxazole (5.9i)



General procedure D was followed using 2-(perfluorophenyl)benzo[*d*]oxazole (142.6 mg, 0.5 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (62.4 mg, 0.2 mmol), TMSCl (76 µL, 0.6 mmol) and THF (0.5 mL) was used.

General isolation method F was followed to isolate **5.9i**. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0-5 cv, 0-5% EtOAc for 5-17 cv, 5% EtOAc for 17-21 cv and ramped to 100% EtOAc for 21-24 cv and then held at 100% EtOAc for 24-25 cv) on a 40 g silica column to afford **5.9i** in 90% yield (136 mg, 0.45 mmol) as a yellow solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -136.6 – -136.7 (m, 2F), -139.2 – -139.3 (m, 2F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.67 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.51 – 7.42 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.5, 150.4, 145.3 (ddt, *J* = 261.1, 14.8, 4.7 Hz), 146.1 – 143.1 (m), 141.0, 126.7, 125.2, 120.9, 115.5 (t, *J* = 18.9 Hz), 111.0, 107.0 (t, *J* = 13.6 Hz). FT-IR cm^{-1} 3030, 1449. GC/MS (*m/z*, relative intensity) 303 (M+2, 20), 301 (M+, 60). Mp 130-131 °C.

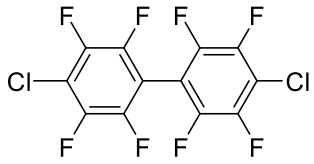
Synthesis of 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]thiazole (5.9j)



General procedure D was followed using 2-(perfluorophenyl)benzo[*d*]thiazole (75.3 mg, 0.25 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (62.4 mg, 0.2 mmol), TMSCl (63.5 µL, 0.5 mmol) and THF (0.5 mL) was used.

General isolation method F was followed to isolate **5.9j**. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 10 cv, 0-10% EtOAc for 10-27 cv, 10% EtOAc for 27-33 cv and ramped to 100% EtOAc for 33-35 cv and then held at 100% EtOAc for 35-37 cv) on a 40 g silica column to afford **5.9j** in 85% yield (67.4 mg, 0.21 mmol) as a yellow solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -138.0 – -138.1 (m, 2F), -139.6 – -139.8 (m, 2F). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.55 (dt, *J* = 30.0, 7.2 Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.8, 146.5 – 145.5 (m), 143.8 – 143.1 (m), 135.6 (t, *J* = 2.7 Hz), 129.0 – 128.2 (m), 126.8, 126.5, 124.2, 121.4, 114.3 (t, *J* = 19.0 Hz), 112.8 (t, *J* = 14.1 Hz). FT-IR cm^{-1} 3061, 2926, 1477. GC/MS (*m/z*, relative intensity) 319 (M+2, 25), 317 (M+, 75). mp 125-126 °C.

Synthesis of 4,4'-dichloro-2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl (5.9k)

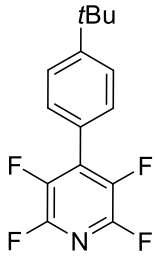


General procedure D was followed using perfluoro-1,1'-biphenyl (133.6 mg, 0.40 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (129.8 mg, 0.40 mmol), TMSCl (121.8 µL, 0.96 mmol) and THF (0.4 mL) was used.

General isolation method F was followed to isolate **5.9k**. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 20 cv, 0-15% EtOAc for 20-27 cv and ramped to 100% EtOAc for 27-28 cv and then held at 100% EtOAc for 28-34 cv) on a 40 g silica column to afford **5.9k** in 45% yield (65 mg, 0.18 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -136.9 – -137.0 (m, 4F), -139.1 – -139.2 (m, 4F). ^{13}C NMR (101 MHz,

Chloroform-*d*) δ 145.5 (d, *J* = 14.2 Hz), 143.0 (d, *J* = 12.7 Hz), 115.0 (t, *J* = 18.6 Hz), 105.2 (t, *J* = 14.2 Hz). FT-IR cm^{-1} 1457, 1246, 720. GC/MS (*m/z*, relative intensity) 368 (M+2, 66), 366 (M+, 100). mp 96-98 °C.

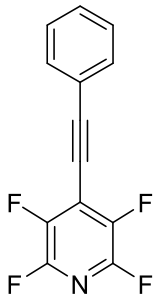
Synthesis of 4-(4-(*tert*-butyl)phenyl)-2,3,5,6-tetrafluoropyridine (5.12a)



5.12a was synthesized starting from pentafluoropyridine as the starting material. **General procedure D** was followed using pentafluoropyridine (110 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (124.8 mg, 0.4 mmol), TMSCl (152 µL, 1.2 mmol) and THF (1.0 mL) was used to afford a crude reaction containing 4-chloro-2,3,5,6-tetrafluoropyridine **(5.9a).** After reaction completion as judged by ^{19}F NMR, the reaction was cooled down to rt. This material was taken to the next step without further purification. In a flame dried vial under argon, the crude material (0.2 mL, 0.2 mmol) was added followed by (4-(*tert*-butyl)phenyl)boronic acid (42.7 mg, 0.24 mmol) and triphenyl phosphine (4.5 mg, 0.02 mmol), 2 M aqueous K_2CO_3 (0.2 mL, 0.378 mmol) and DME (0.2 mL). The vial was capped and the mixture was degassed *via* argon bubbling for 5 min at 0 °C (to avoid evaporation of 4-chloro-2,3,5,6-tetrafluoropyridine **(5.9a)**). Then, $Pd(OAc)_2$ was added and the degassing was continued again for 5 min. The reaction was heated at 110 °C overnight. Next day, the reaction was cooled to rt and passed through a celite pad and eluted with DCM (5 mL). Then, the volatiles were removed *via* rotavap. The residue was treated with DCM (10 mL) and washed with water (3 x 5 mL). Then the DCM layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using hexane:DCM (0% DCM for 0-5 cv, 0-3% DCM for 5-15 cv, 3% DCM for 15-27 and ramped to 100% for 27-35 cv and then held at 100% DCM for 35-37 cv) on a 40 g silica column. The isolated fraction which contained an unidentified byproduct was further purified by a reverse phase chromatography using water:MeCN (10% MeCN for 1 cv and ramped to 100% MeCN for 1-22 cv and then held at 100% MeCN for 22-25 cv) on a 26 g C-18 column to

afford **5.12a** in 70% yield (39.6 mg, 0.14 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -90.9 – -91.2 (m), -145.2 – -145.4 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.54 (m, 2H), 7.48 (dt, *J* = 8.6, 1.8 Hz, 2H), 1.38 (s, 9H), 7.59 – 7.54 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.2, 144.2 (dddd, *J* = 244.6, 17.0, 13.4, 2.8 Hz), 141.0 – 137.9 (m), 133.6 (tt, *J* = 14.5, 2.8 Hz), 129.7 (t, *J* = 2.5 Hz), 126.1, 123.1, 35.1, 31.3. FT-IR cm^{-1}2970, 1450. GC/MS (*m/z*, relative intensity) 283 (M+, 15), 268 (95), 240 (60). mp 104-105 °C.

Synthesis of 2,3,5,6-tetrafluoro-4-(phenylethynyl)pyridine (5.12b)

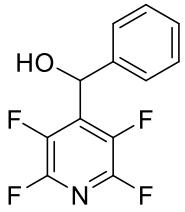


5.12b was synthesized by following a modified literature procedure (Huang, H.; Liu, H.; Jiang, H.; Chen, K. *J. Org. Chem.* **2008**, *73*, 6037) starting from 4-chloro-2,3,5,6-tetrafluoropyridine **(5.9a)**. In a flame dried microwave vial under argon the **5.9a** (13.7 µL, 0.1 mmol) was added followed by phenylacetylene (13.2 µL, 0.12 mmol) and Cs_2CO_3 (32.5 mg, 0.1 mmol). Then, the capped vial was moved to the glovebox and $PdCl_2(pph_3)_2$ (1.4 mg, 0.002 mmol) and *t*Bu_3P (0.81 mg, 0.004 mmol) were added. The mixture was recapped and it was removed from the glovebox. Degassed DMF (0.4 mL) was added, followed by DBU (1,8-Diazabicyclo(5.4.0)undec-7-ene) (1.5 µL, 0.01 mmol) and the reaction mixture was degassed *via* argon bubbling for 5 min at 0 °C (to avoid evaporation of 4-chloro-2,3,5,6-tetrafluoropyridine). Then, the reaction was placed in a microwave reactor (Biotage initiator, 200 °C, 10 min). After cooling to rt, the reaction was diluted with EtOAc and filtered through a pad of celite. The filtrate was rotavaped and hexane (20 mL) was added. The hexane layer was washed with brine (3 x 10 mL). The combined aqueous phase was extracted with hexane (2 x 10 mL) and the combined organic phase was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo*. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 20 cv, 0-12% EtOAc for 20-30 cv, 12% EtOAc for 30-33 cv and ramped to 100% EtOAc for 33-35 cv and then held at 100% EtOAc for 35-37 cv) on a 40 g silica column to afford **5.12b** in 80% yield (20.1 mg, 0.08 mmol) as a white solid. ^{19}F NMR (376

MHz, Chloroform-*d*) δ -90.4 – -90.6 (m), -138.2 – -138.5 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 7.2 Hz, 2H), 7.45 (dt, *J* = 14.5, 7.0 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.1 – 141.9 (m), 143.4 – 140.2 (m), 132.3, 130.6, 128.7, 120.6, 106.7 (t, *J* = 3.5 Hz). FT-IR cm^{-1} 2922, 2215, 735. GC/MS (*m/z*, relative intensity) 251 (M+, 100), 231 (10). mp 136-137 ^{o}C.

Synthesis of (perfluoropyridin-4-yl)(phenyl)methanol (5.12c)

5.12c was synthesized starting from pentafluoropyridine as the starting material. **General procedure D** was followed using pentafluoropyridine (110 µL, 1.0 mmol), *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium chloride (124.8 mg, 0.4 mmol), TMSCl (152 µL, 1.2 mmol) and THF (1.0 mL) was used to afford a crude reaction containing 4-chloro-2,3,5,6-tetrafluoropyridine **(5.9a).** After reaction completion as judged by ^{19}F NMR, the reaction was cooled to rt. An aliquot (0.5 mL, 0.5 mmol) was taken out and diluted with pentane (5.0 mL) and it was washed with 1M HCl (3 x 5 mL). The pentane layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. This material was taken to the next step without further purification.



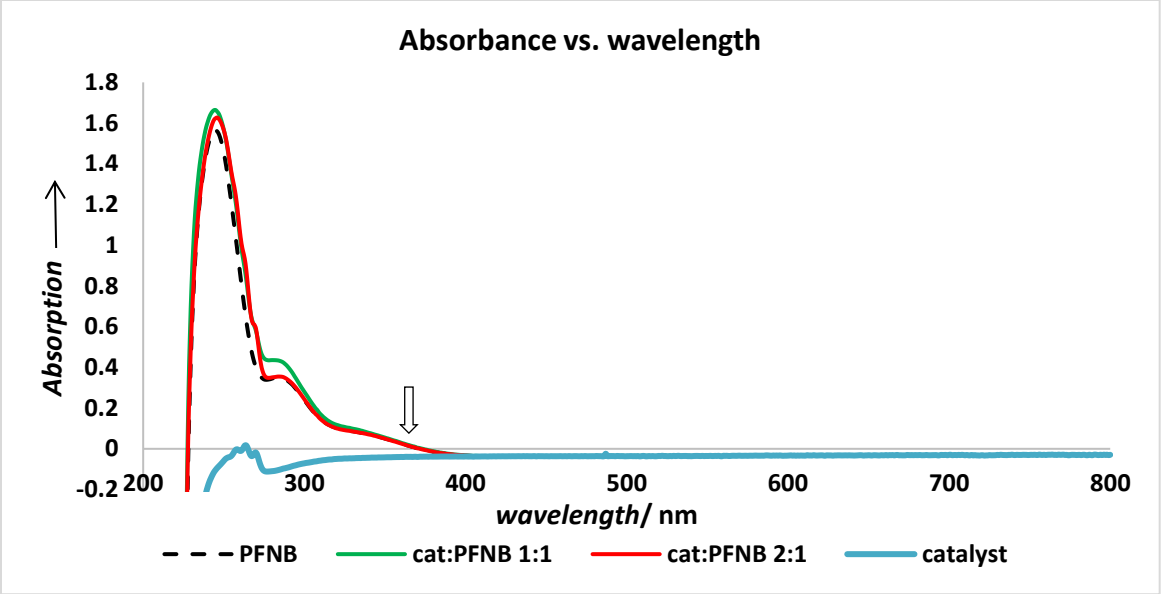
In a flame dried vial under argon the crude material after workup (0.5 mmol) was added followed by THF (1.4 mL) and it was cooled to -78 ^{o}C. Then, BuLi (0.53 mL, 0.84 mmol, ~1.6 M solution in hexane) was slowly added over 10 min and stirring was continued for 20 min at -78 ^{o}C. To the above mixture, benzaldehyde (86 µL, 0.84 mmol) was added as a one portion and it was allowed to warm to rt slowly while stirring. After 45 min, the reaction was quenched by adding sat. NH_4Cl (3.0 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). Combined organic phase was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo*. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 5 cv, 0-10% EtOAc for 5-10 cv, 10% EtOAc for 10-15 cv, 10-20% EtOAc for 15-17 cv, 20% EtOAc for 17-22 cv and

ramped to 100% EtOAc for 22-24 cv and then held at 100% EtOAc for 24-26 cv) on a 40 g silica column to afford **5.12c** in 62% yield (80.0 mg, 0.31 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -90.0 – -90.2 (m), -143.9 – -144.1 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 (dt, *J* = 12.5, 6.1 Hz, 5H), 6.27 (s, 1H), 2.99 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.4 – 142.2 (m), 141.3 – 138.1 (m), 139.3, 135.6 (t, *J* = 13.1 Hz), 129.2, 129.0, 125.7, 68.5. FT-IR cm^{-1} 3356, 2914, 1472. GC/MS (*m/z*, relative intensity) 257 (M+, 20), 178 (15). mp 100-101 ^{o}C

Evidence for pre-complexation between perfluoroarene and $BnBu_3NCl$

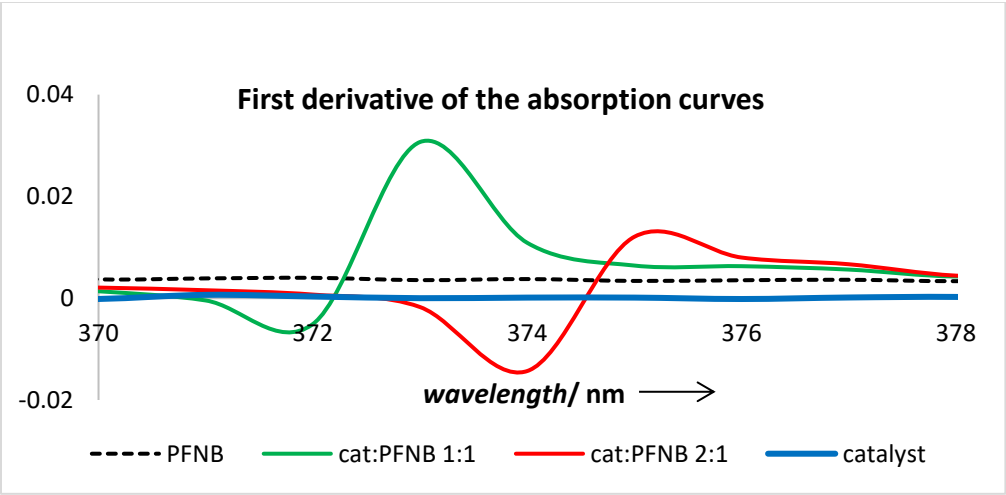
UV-vis experiment

A UV-vis experiment was carried using DCM as the solvent, in which UV-vis spectra were collected for both the individual components and the mixed components, and then compared. The experiment was carried out by mixing pentafluoronitrobenzene (PFNB) and $BnNBu_3Cl$ (1:1 and 1:2 molar ratio) and PFNB:$BnNBu_3Cl$:TMSCl (1:2:2 molar ratio) in DCM. Pentafluoronitrobenzene (PFNB) (0.0064 mmol, 0.8 µL) and $BnBu_3NCl$ (catalyst) (0.0064 mmol, 2.0 mg) were separately dissolved in DCM (20 mL, 3.2 x 10^{-4} M) to obtain individual solutions. To obtain the two component 1:1 mixture PFNB (0.0064 mmol, 0.8 µL) and catalyst (0.0064 mmol, 2.0 mg) were mixed in DCM (20 mL, 3.2 x 10^{-4} M) and the 1:2 mixture was obtained by mixing PFNB (0.0064 mmol, 0.8 µL) and catalyst (0.0128 mmol, 4.0 mg) in DCM (20 mL, 3.2 x 10^{-4} M). Pentafluoronitrobenzene (PFNB) (0.0064 mmol, 0.8 µL), $BnBu_3NCl$ (catalyst) (0.0128 mmol, 4.0 mg) and trimethylsilyl chloride (TMSCl) (0.0128 mmol, 1.6 µL) were mixed in DCM (20 mL, 3.2 x 10^{-4} M) to obtain the three component mixture. Then the UV-vis spectra were obtained. Following is the overlapped plot showing a new weak absorption band emergence at around 370-380 nm.

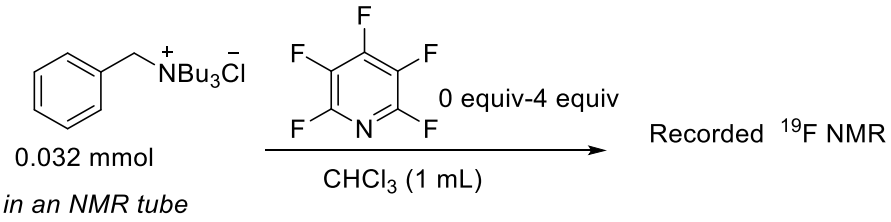


First derivative of the absorption curves

Overlap of PFNB's absorption band with the newly formed band obscures identification of the maximum absorption wavelength (λ_{max}). Therefore, we performed a first derivative analysis which allowed us to identify a new red-shifted λ_{max} of both the 1:1 and 2:1 catalyst:PFNB complexes. The observation of two different λ_{max} values also supports the formation of two distinct types of complexes. The first derivative analysis of above reported absorption curves are shown below.



NMR titration experiment; pentafluoropyridine (PFP) and $BnNBu_3Cl$ in $CHCl_3$

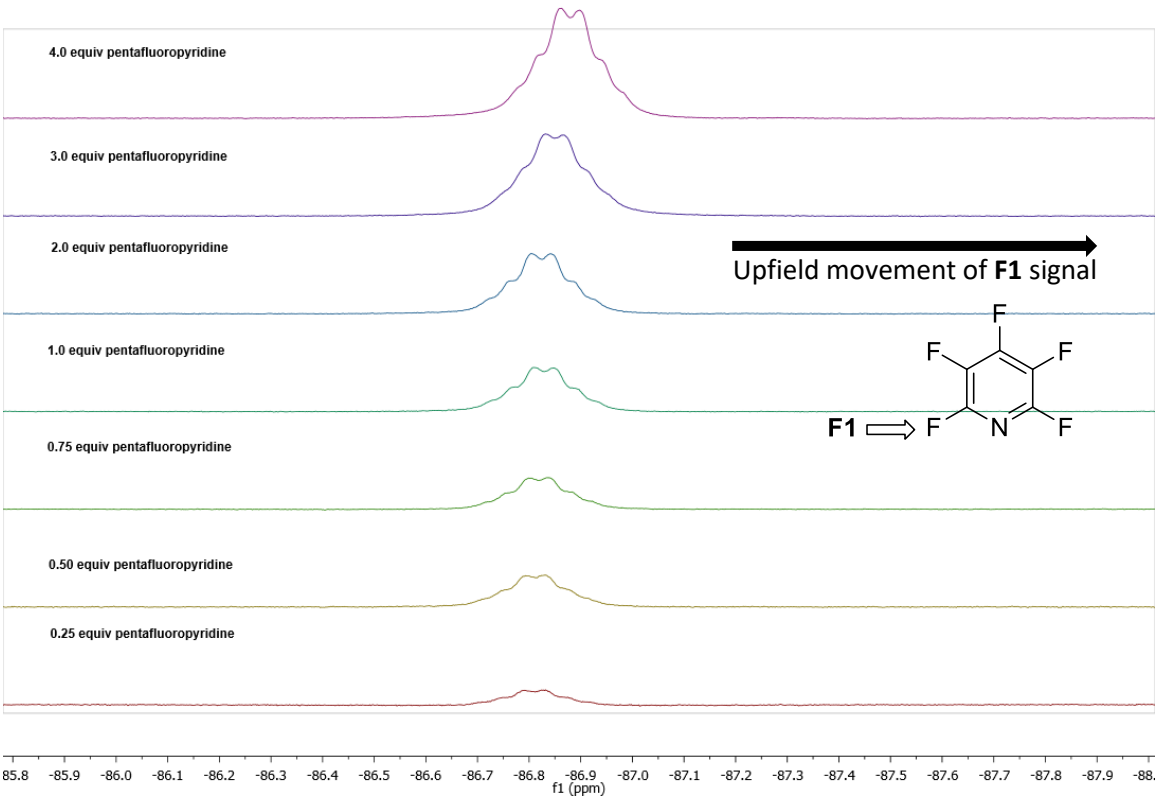


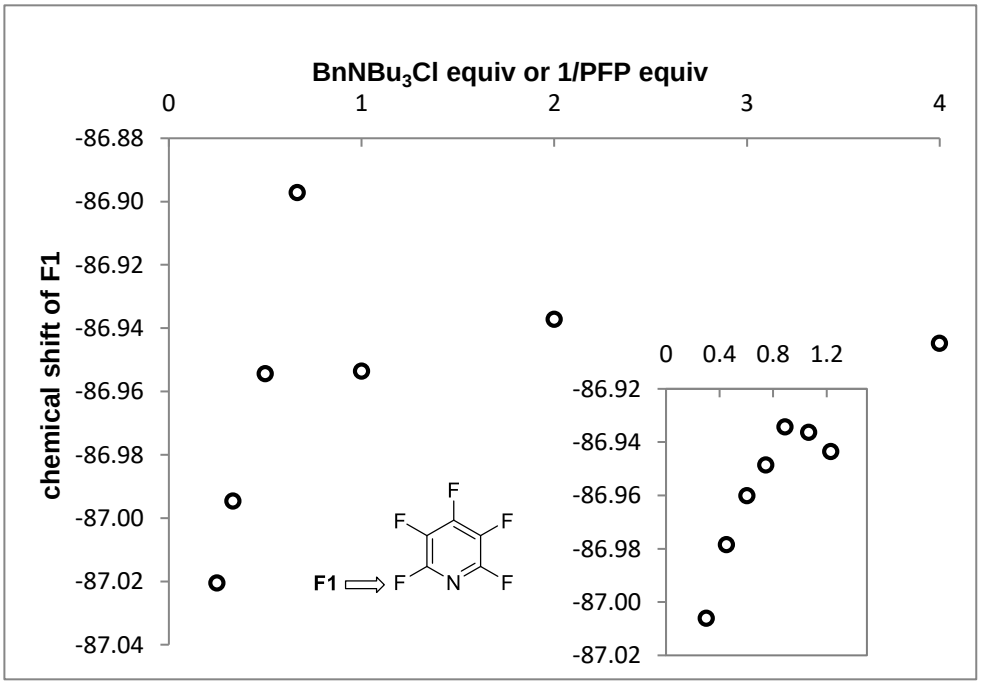
NMR titration was carried out in $CHCl_3$. Two separate stock solutions of $BnBu_3NCl$ and PFP were prepared by dissolving $BnBu_3NCl$ (0.064 M, 99.8 mg in 5.0 mL of $CHCl_3$) and PFP (0.256 M, 140 µL in 5.0 mL of $CHCl_3$). In eight separate NMR tubes above two solutions were added according to the following table to obtain samples with constant amount of $BnBu_3NCl$ and different amounts of PFP. All the samples were topped up to 1 mL by adding $CHCl_3$ according to the table.

equiv of PFP	mmol of PFP	volume PFP solution added (µL)	volume $BnBu_3NCl$ solution added (mL)	volume $CHCl_3$ added (mL)
0.0	0	0.0	0.50	0.50
0.25	8×10^{-3}	31.2	0.50	0.47
0.50	1.6×10^{-2}	62.5	0.50	0.44
1.0	3.2×10^{-2}	125.0	0.50	0.38
1.5	4.8×10^{-2}	187.5	0.50	0.31
2.0	6.4×10^{-2}	250.0	0.50	0.25
3.0	9.6×10^{-2}	375.0	0.50	0.13

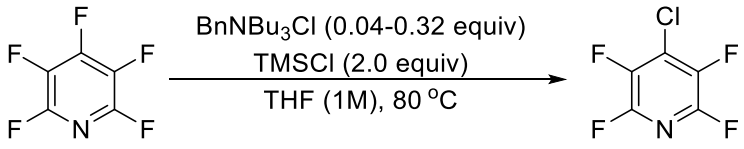
4.0	1.3×10^{-1}	500.0	0.50	0.0

For referencing purposes a sealed glass capillary containing $CDCl_3$:trifluoroacetic acid (100:1 v/v) was placed in each NMR tube and ^{19}F NMR were obtained. Upfield shifts for all three fluorine atoms of pentafluoropyridine were observed. Chemical shift of the fluorine atom at -86 ppm was plotted as a function of the equivalents of $BnBu_3NCl$. The graphs indicate an upfield shift of the fluorine signal with increasing $BnNBu_3Cl$ concentration up to about 0.7 equiv. However, between 0.7-2.0 equivalents, the fluorine signals moved down-field. Finally, after 2.0 equivalents of $BnNBu_3Cl$, the ^{19}F chemical shifts become constant as displays in the graph below. Initially, we thought the data point at 0.7 is an outlier. However, we performed another titration experiment to collect more data points in the region between 0.3-1.2 equiv of $BnBu_3NCl$ which clearly shows a maximum at around 0.8 equiv. Then the chemical shift started decrease with increasing $BnNBu_3Cl$. These results are consistent with initial formation of a 1:1 and then a 1:2 complex between the fluoroarene and the catalyst.


4.0 equiv pentafluoropyridine
3.0 equiv pentafluoropyridine
2.0 equiv pentafluoropyridine
1.0 equiv pentafluoropyridine
0.75 equiv pentafluoropyridine
0.50 equiv pentafluoropyridine
0.25 equiv pentafluoropyridine
Upfield movement of F1 signal
F1
F
F
F
F
N
F
-85.8 -85.9 -86.0 -86.1 -86.2 -86.3 -86.4 -86.5 -86.6 -86.7 -86.8 -86.9 -87.0 -87.1 -87.2 -87.3 -87.4 -87.5 -87.6 -87.7 -87.8 -87.9
f1 (ppm)

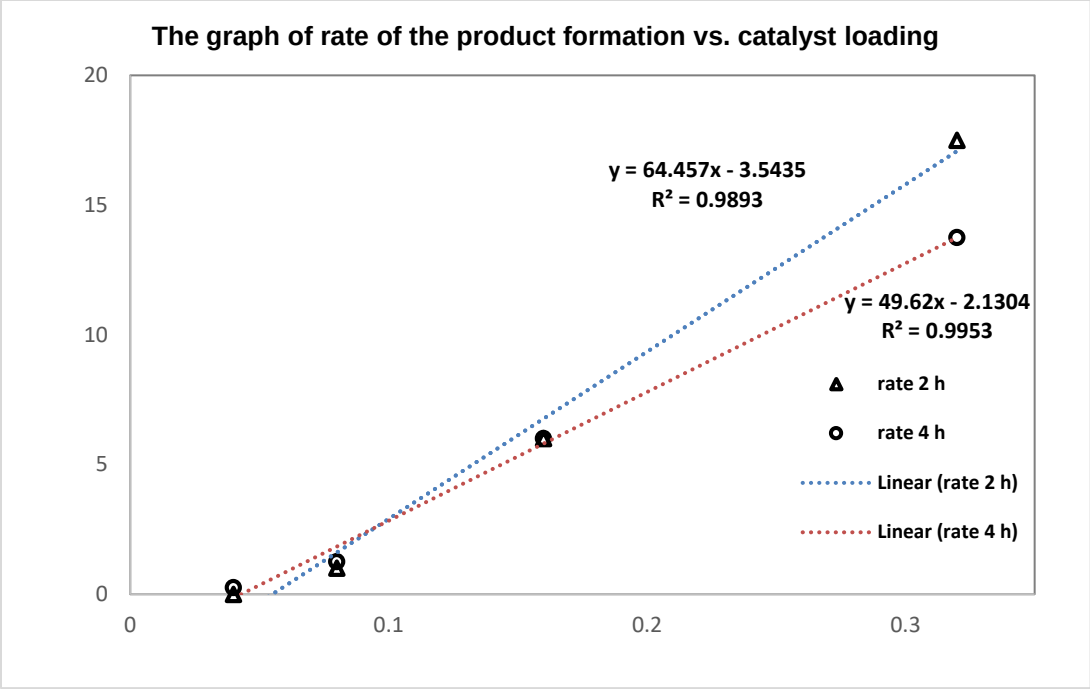

BnNBu3Cl equiv or 1/PFP equiv
0
1
2
3
4
chemical shift of F1
-86.88
-86.90
-86.92
-86.94
-86.96
-86.98
-87.00
-87.02
-87.04
F1
F
F
F
F
N
F
0
0.4
0.8
1.2
-86.92
-86.94
-86.96
-86.98
-87.00
-87.02

Kinetic study supporting the formation of a 2:1 complex between the catalyst and pentafluoropyridine



A kinetic study was done to determine the rate dependency on the catalyst. A sealable vial was charged with the fluoroarene (1.0 equiv), $BnNBu_3Cl$ (0.04 equiv), THF (1.0 M), TMSCl (2.0 equiv) and sealed. The reaction was stirred while heating at 80 °C in an oil bath. Aliquots were taken out after 2 h and 4 h and diluted with $CDCl_3$ to monitor the conversion by ^{19}F NMR. The reaction was repeated with 0.08, 0.16 and 0.32 equiv of $BnNBu_3Cl$. Then, initial rates were calculated. The rate of product formation was plotted against the catalyst loading and is shown below.

Catalyst loading	Conv % after 2 h	rate (2 h)	Conv % after 4 h	rate (4 h)
0.04	0	0	1	0.25
0.08	2	1	5	1.25
0.16	12	6	24	6
0.32	35	17.5	55	13.75



Initial rate = k [cat]^{a}

After 4 h,

With 0.04 equiv catalyst, rate = 0.25= k [0.04] ^{a}

With 0.08 equiv catalyst, rate = 1.25= k [0.08] ^{a}

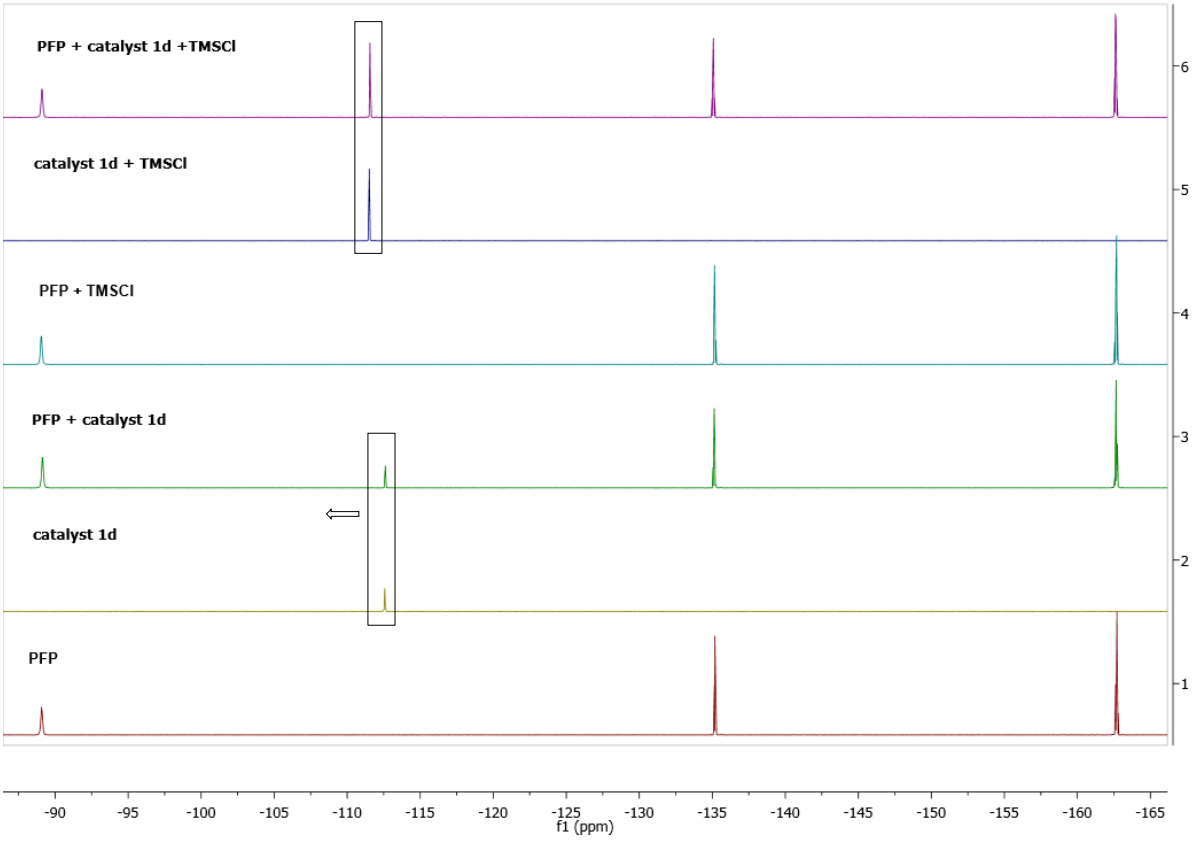
Order of the reaction with respect to the catalyst (a) = 2.3

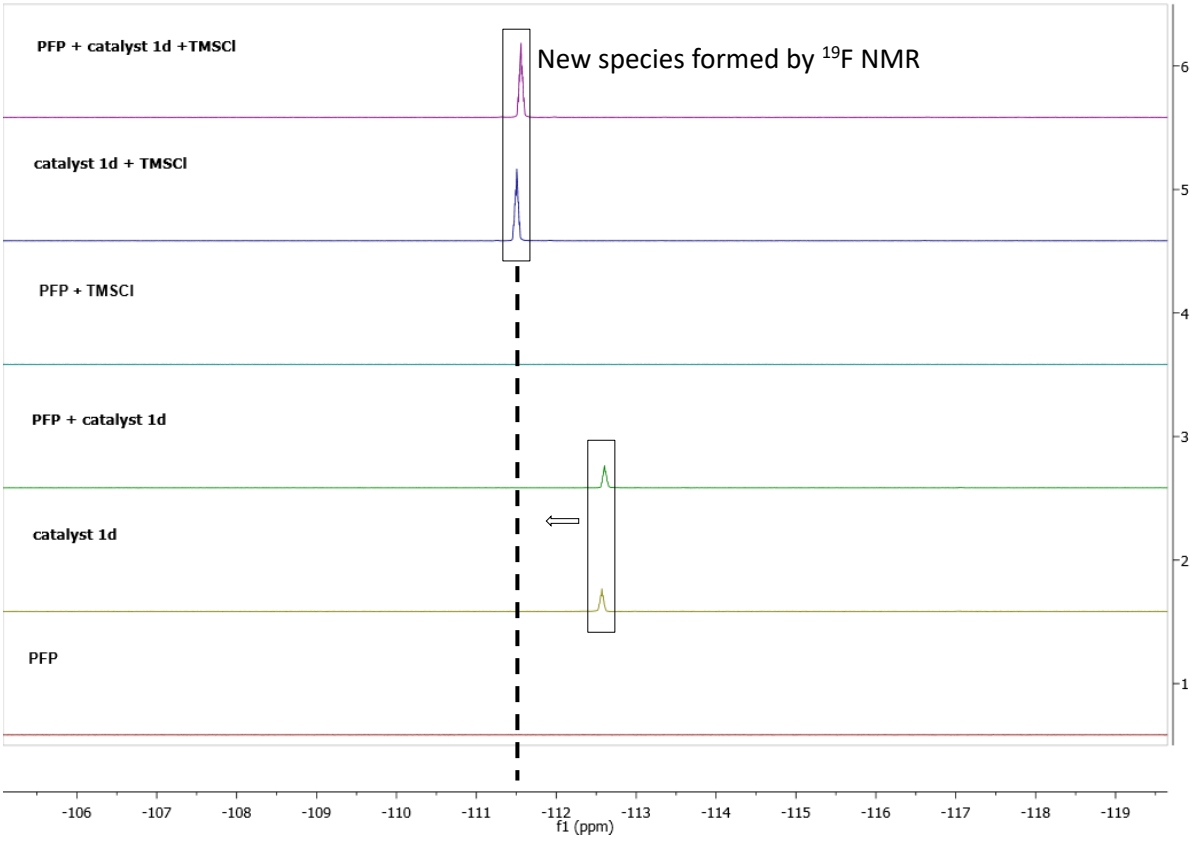
<u>Evidences for the formation of $Me_3SiCl_2^-$</u>

^{19}F NMR evidence

To see individual effects of each reagent in the halogenation reaction the following experiment was carried out. For ease of monitoring catalyst **1d** (4-F-BnNBu$_3$Cl) was chosen such that it could be observed by ^{19}F NMR. NMR spectra were recorded in THF with a sealed C_6D_6 capillary for locking purposes. First, individual ^{19}F NMR spectra of pentafluoropyridine (PFP) and **1d** were recorded (spectra 1 and 2) followed by 1:1 molar mixtures of PFP:**1d** (spectrum 3),

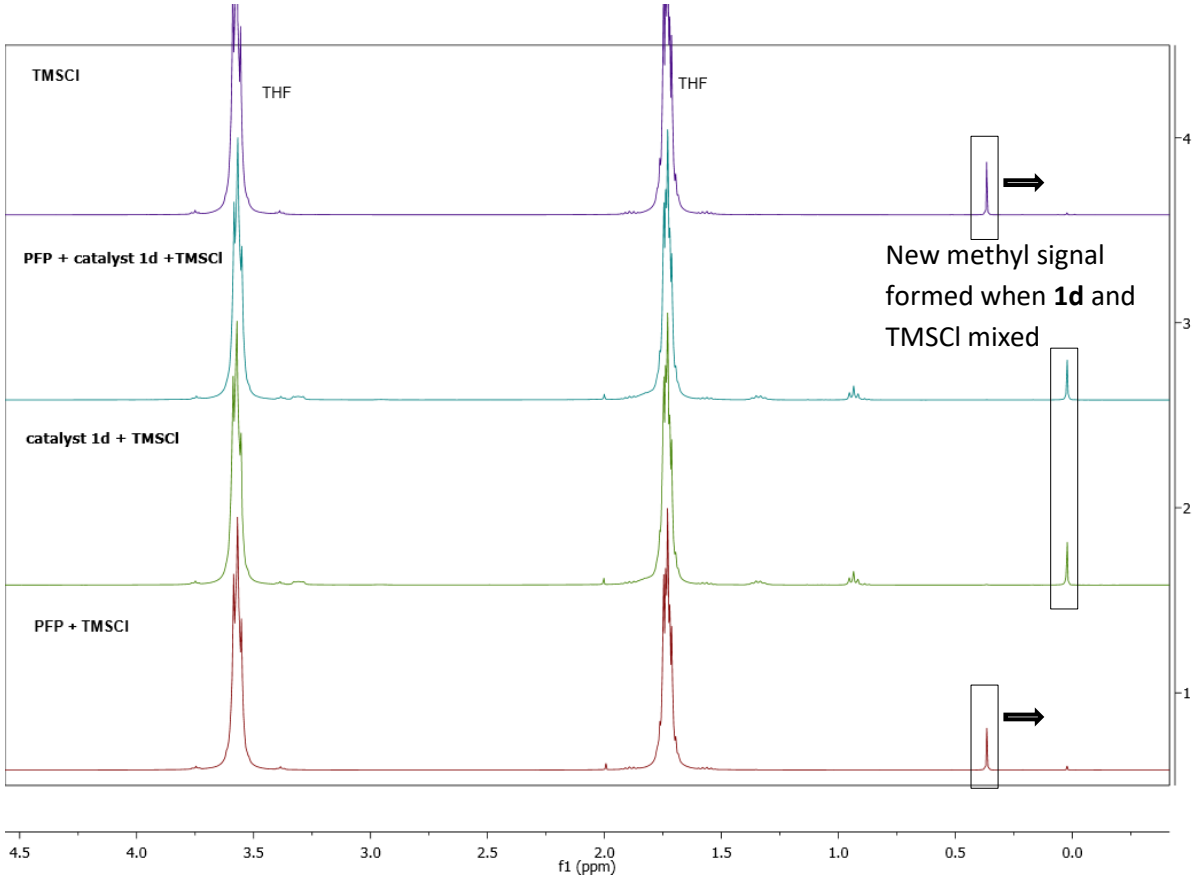
PFP:TMSCl (spectrum 4), **1d**:TMSCl (spectrum 5), and a 1:1:1 molar mixture of PFP:**1d**:TMSCl (spectrum 6). The most significant change was observed when catalyst 1d and TMSCl were mixed (compare spectra 2 *vs.* 5 and 6). This suggests a quantitative formation of a new species between catalyst (**1d**) and TMSCl.





When comparing ^{1}H NMR of above samples, a similar trend was observed. The samples containing catalyst **1d** and TMSCl lead to quantitative formation of a new species which is in agreement with ^{19}F data obtained.

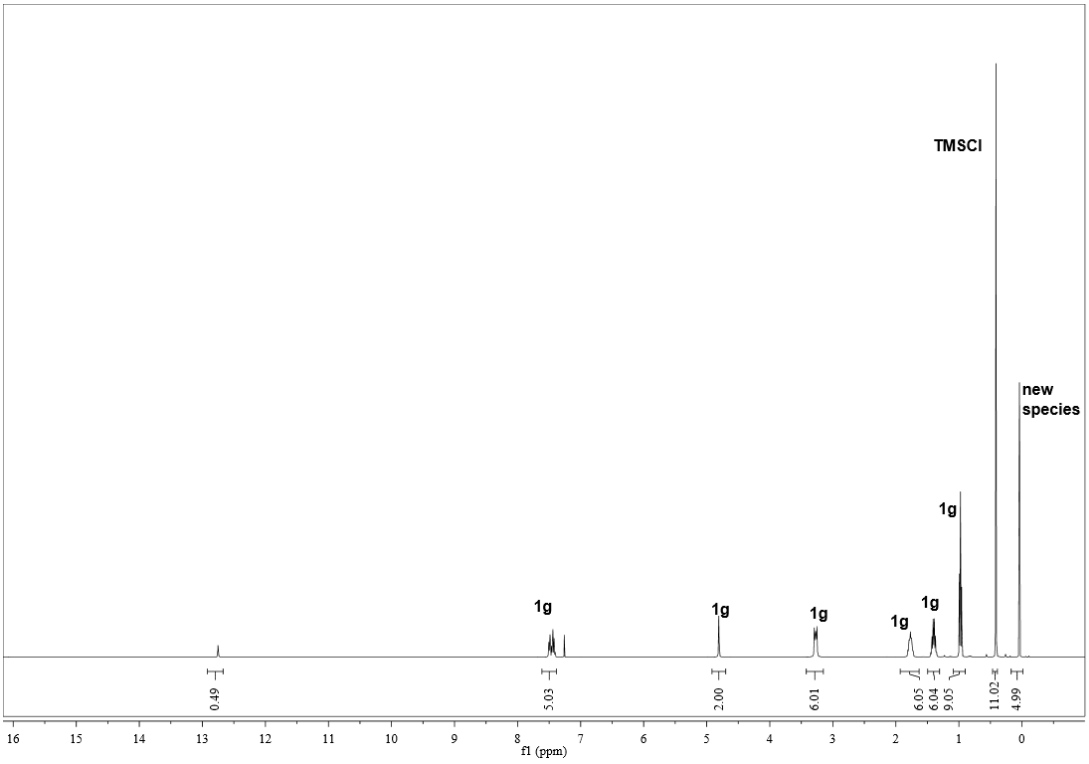
^{1}H NMR evidences



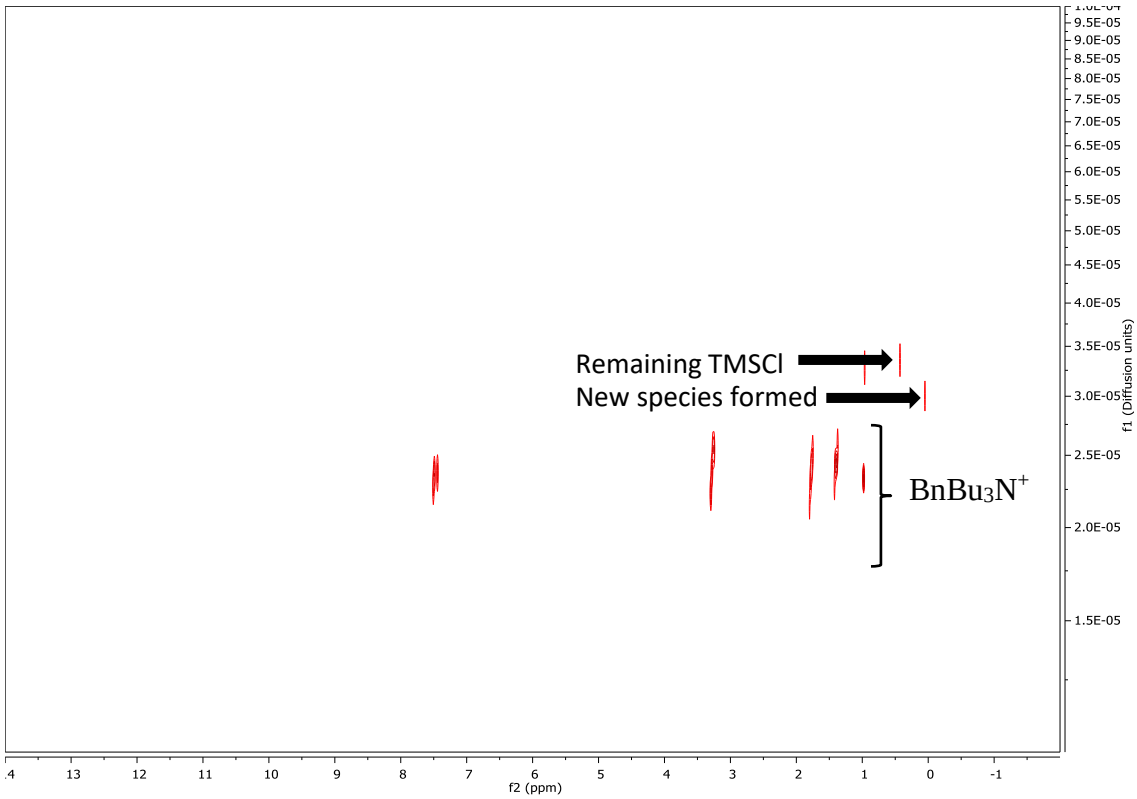
^{1}H DOSY-NMR spectrum

In order to determine the structure of the new species formed we carried out a ^{1}H-DOSY experiment and the molecular mass was obtained by HRMS. For DOSY experiment a NMR sample was prepared by mixing catalyst **1g** (0.025 mmol, 7.79 mg, 1.0 equiv) and TMSCl (0.05 mmol, 6.34 µL, 2.0 equiv) in $CDCl_3$ (0.4 mL). Molecular weight of new species was calculated after plotting ^{1}H-DOSY data.

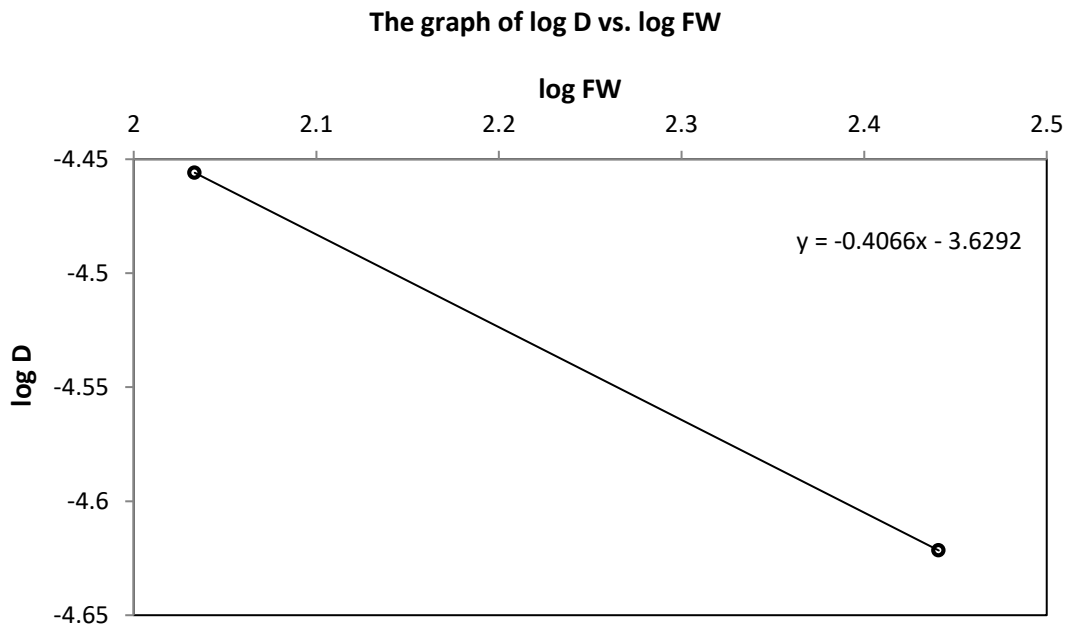
<u>^{1}H NMR after mixing **1g** and TMSCl</u>



^{1}H-DOSY NMR after mixing **1g** and TMSCl



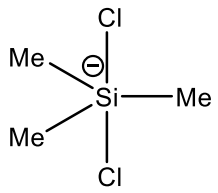
Calculation of unknown formula weight based on diffusion coefficient



y = -0.4066x - 3.6292

D of new species = 3.196 x 10^{-5} cm^2/s at 23 ^oC, log D = -4.495, substituting this for y value in above equation

-4.495 = -0.4066x - 3.6292



x = (-4.495+3.6292)/ (-0.4066) = 135

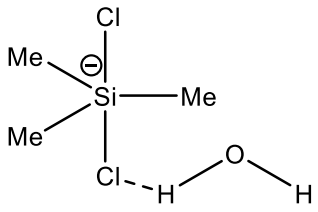
observed molecular weight = 135

calculated molecular weight for $C_3H_9Cl_2Si^-$ = 144

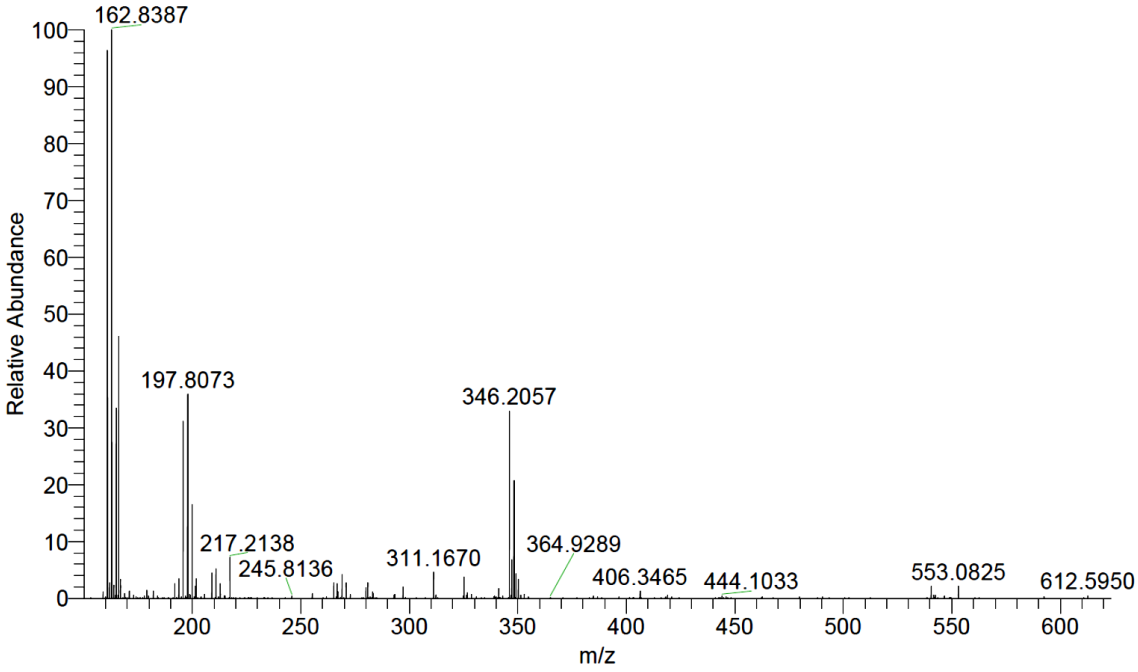
error% = ((144-135)/144

HRMS evidences

HRMS (ESI) of the above mixture (catalyst **1g** (0.025 mmol, 7.79 mg, 1.0 equiv) and TMSCl (0.05 mmol, 6.34 µL, 2.0 equiv)) after being diluted with a matrix of acetone:MeCN (3:2 v/v) shows signals at 160.8419 and 162.8387 and is consistent with a dichlorosilicate.

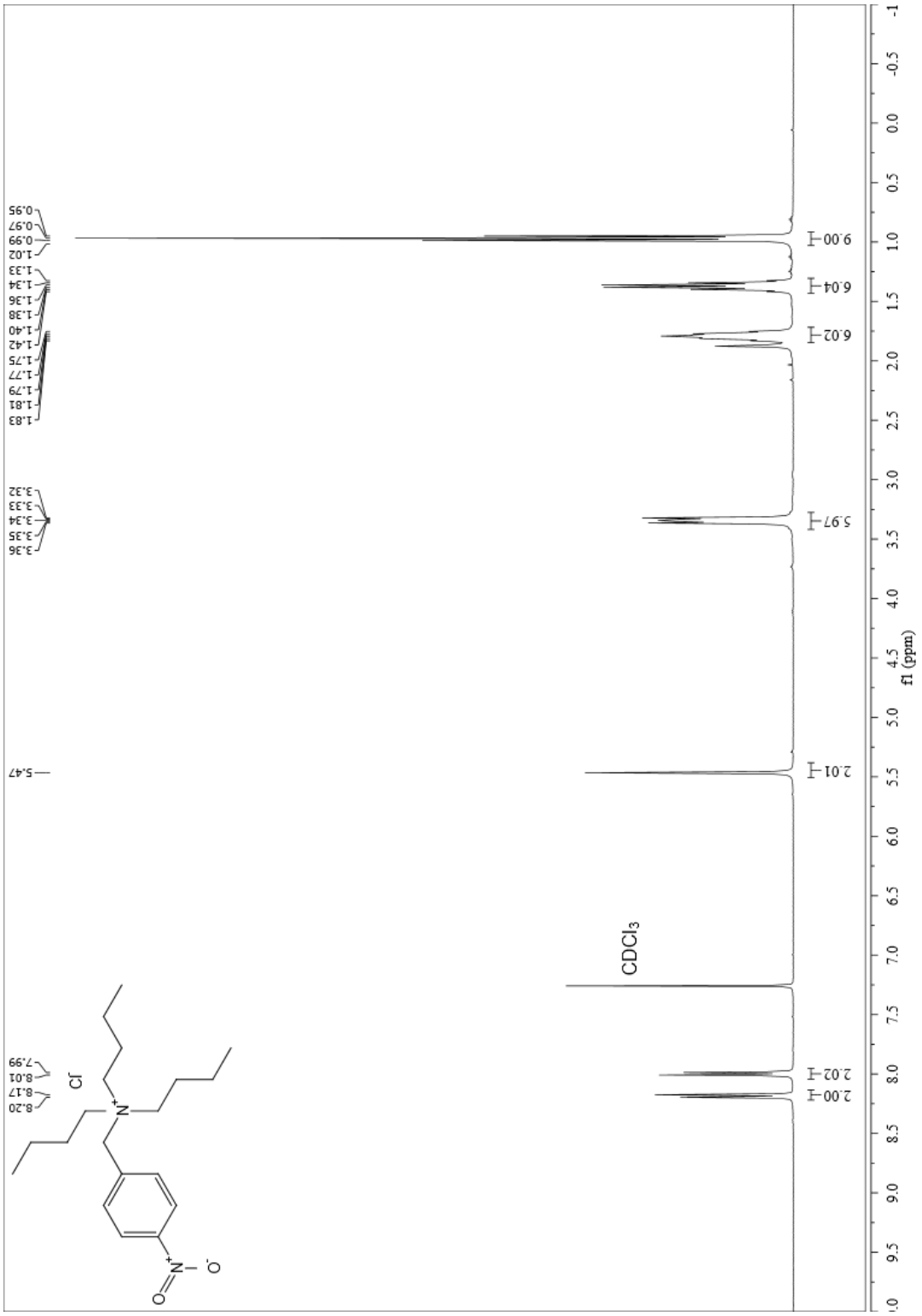


Chemical Formula:
$C_3H_{11}Cl_2OSi^-$
Exact Mass: 161
Molecular Weight: 162

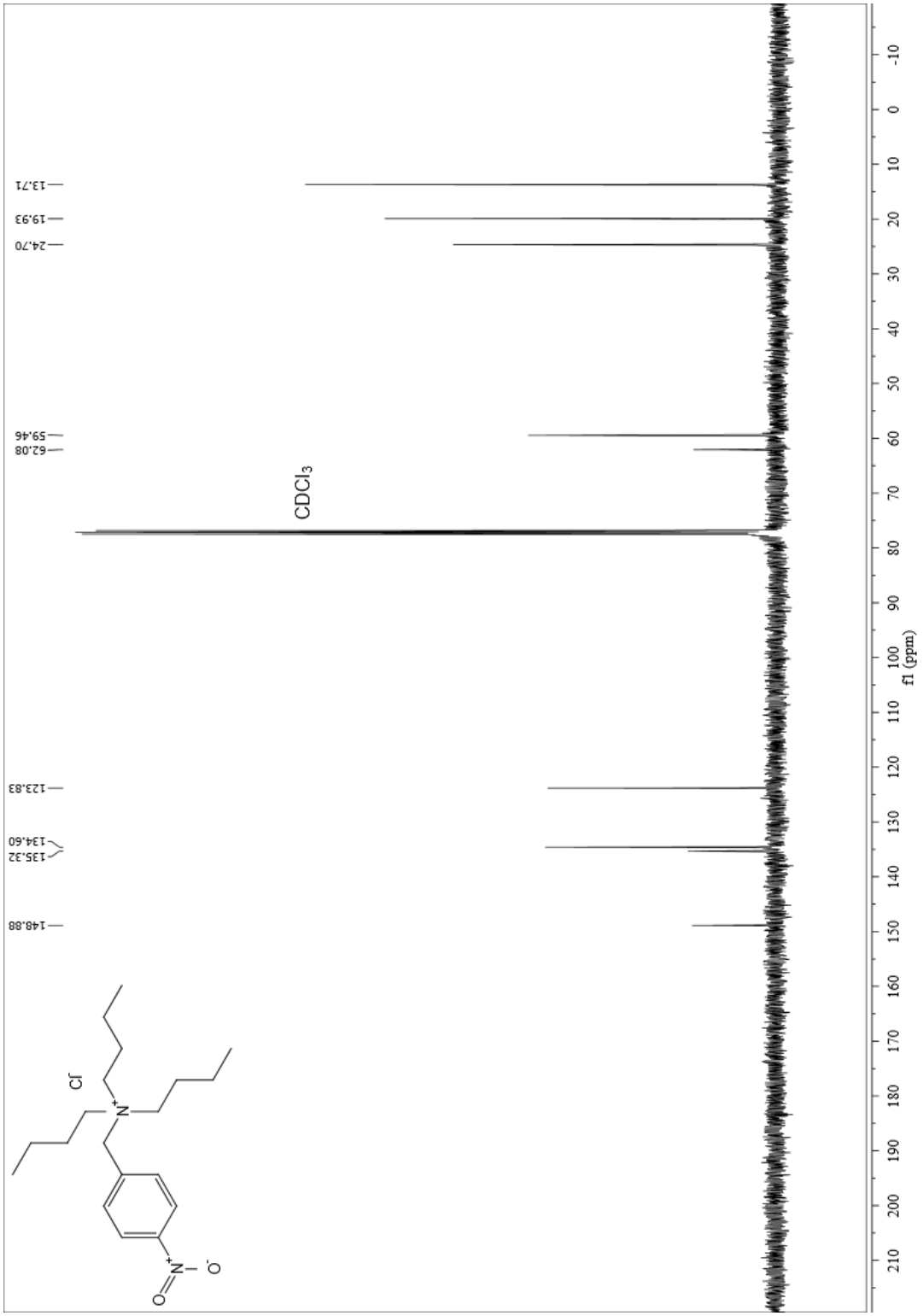


NMR, GC and MS spectra for Chapter V

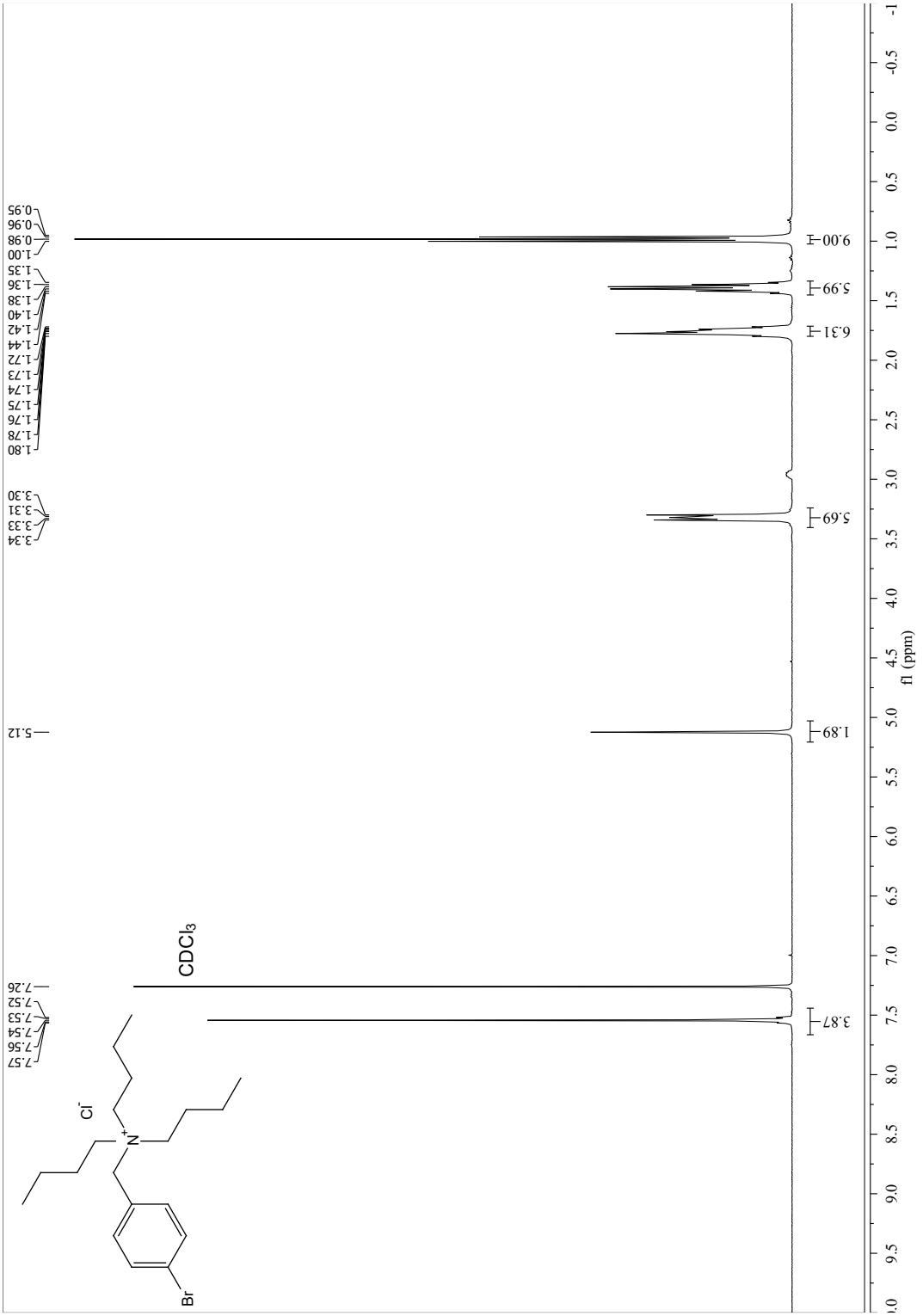
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7a (*N*,*N*-dibutyl-*N*-(4-nitrobenzyl)butan-1-aminium chloride)



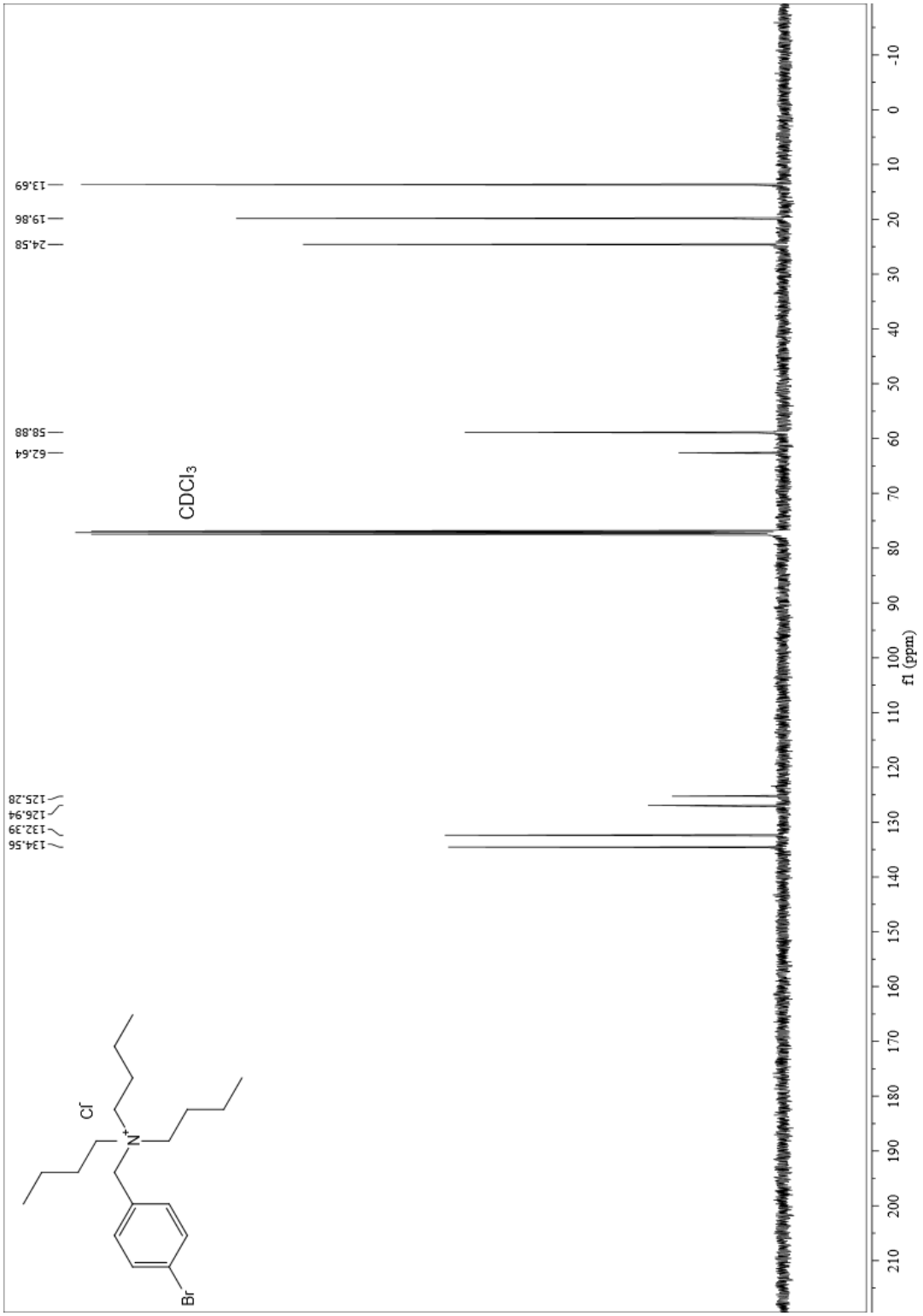
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7a (*N*,*N*-dibutyl-*N*-(4-nitrobenzyl)butan-1-aminium chloride)



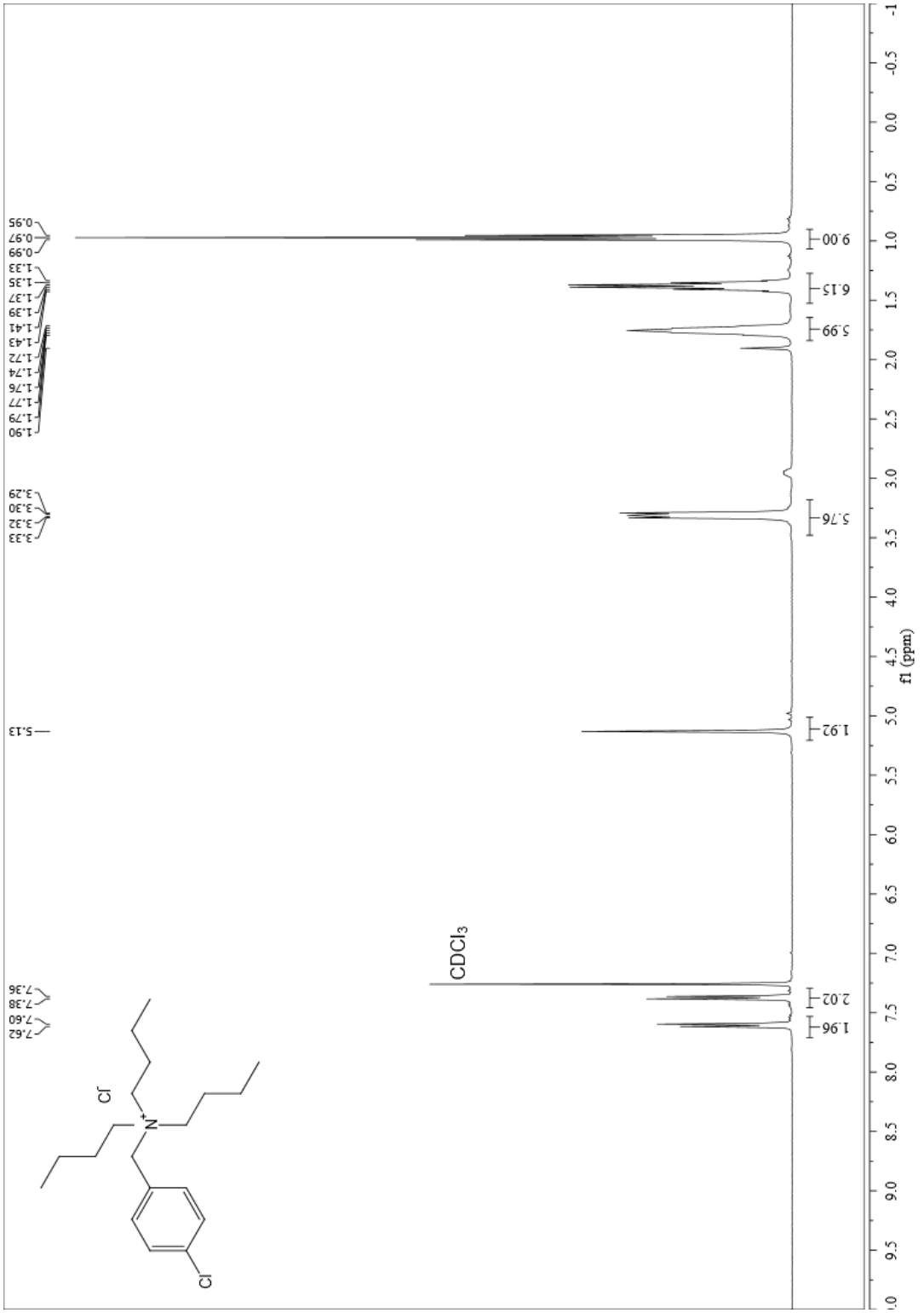
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7b (*N*-(4-bromobenzyl)-*N*,*N*-dibutylbutan-1-aminium chloride)



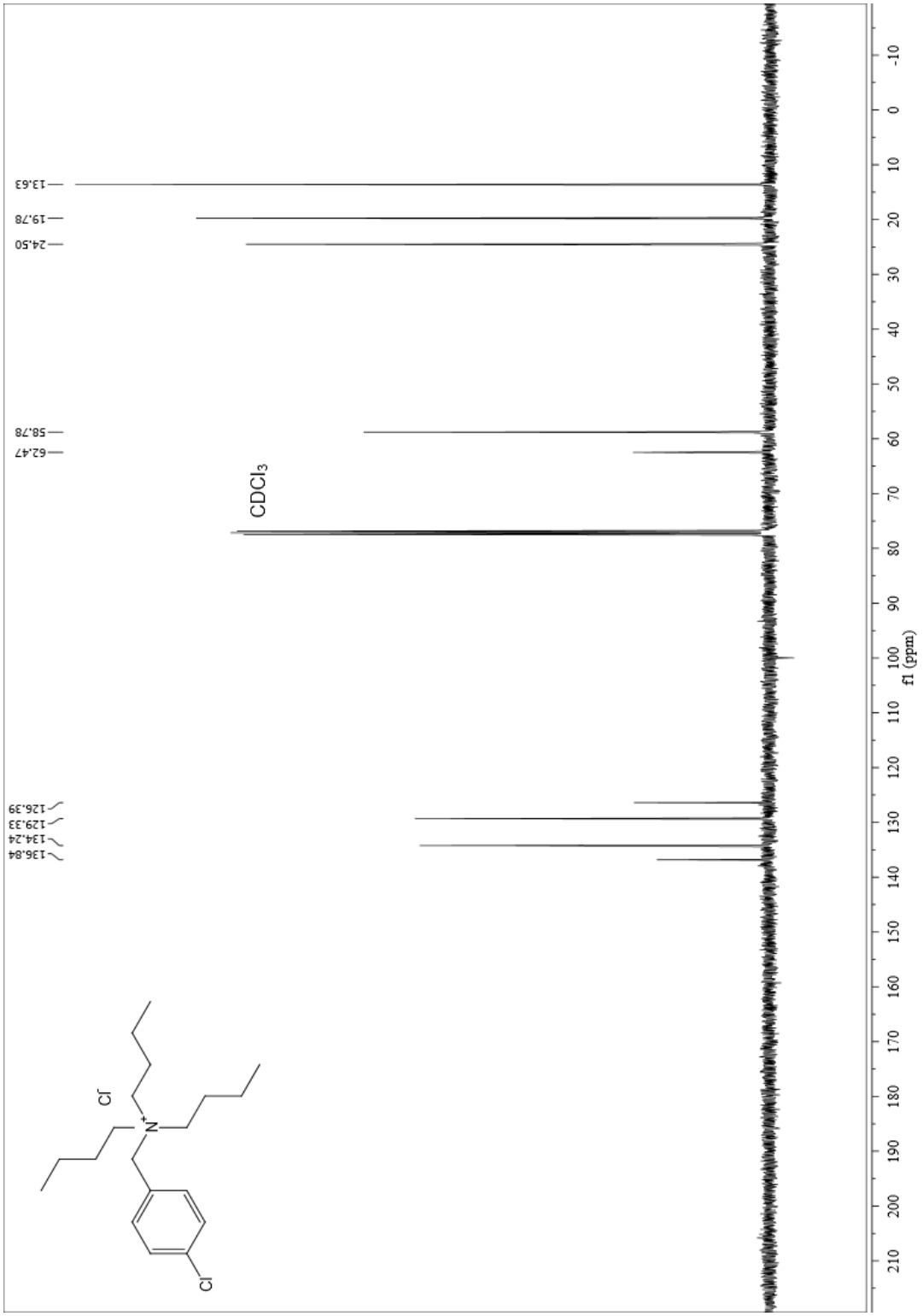
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7b (*N*-(4-bromobenzyl)-*N*,*N*-dibutylbutan-1-aminium chloride)



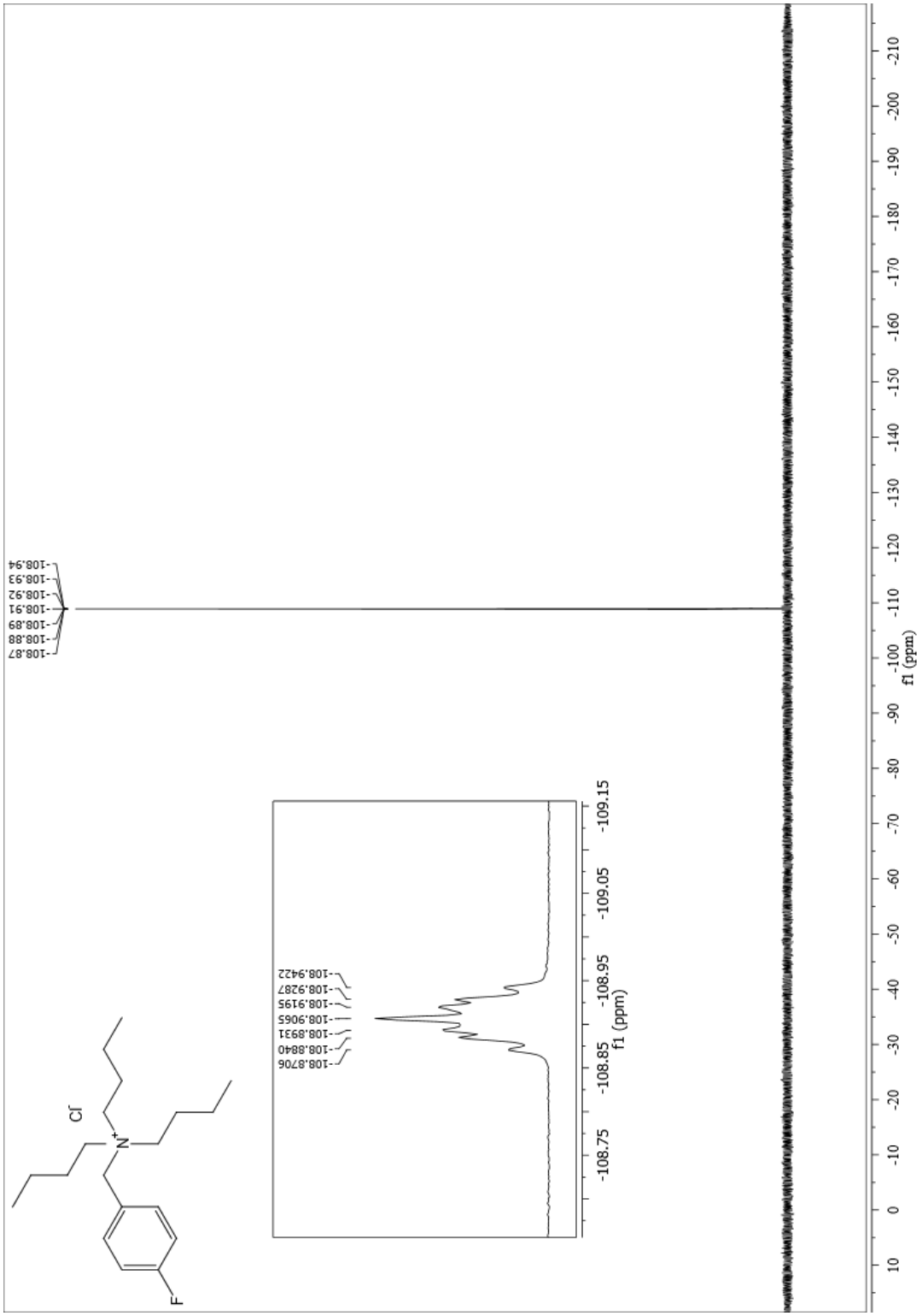
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7c (*N*,*N*-dibutyl-*N*-(4-chlorobenzyl)butan-1-aminium chloride)



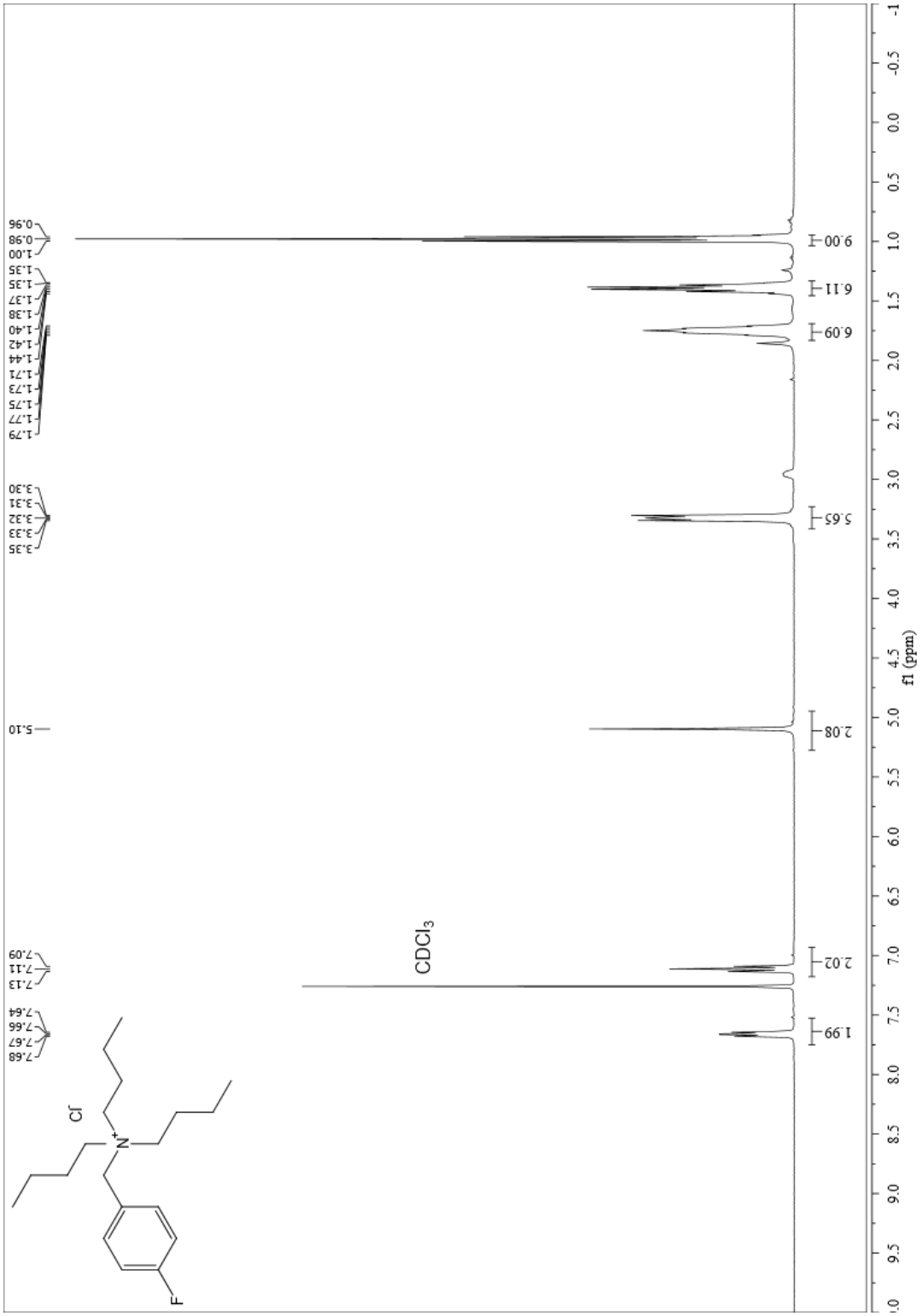
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7c (*N*,*N*-dibutyl-*N*-(4-chlorobenzyl)butan-1-aminium chloride)



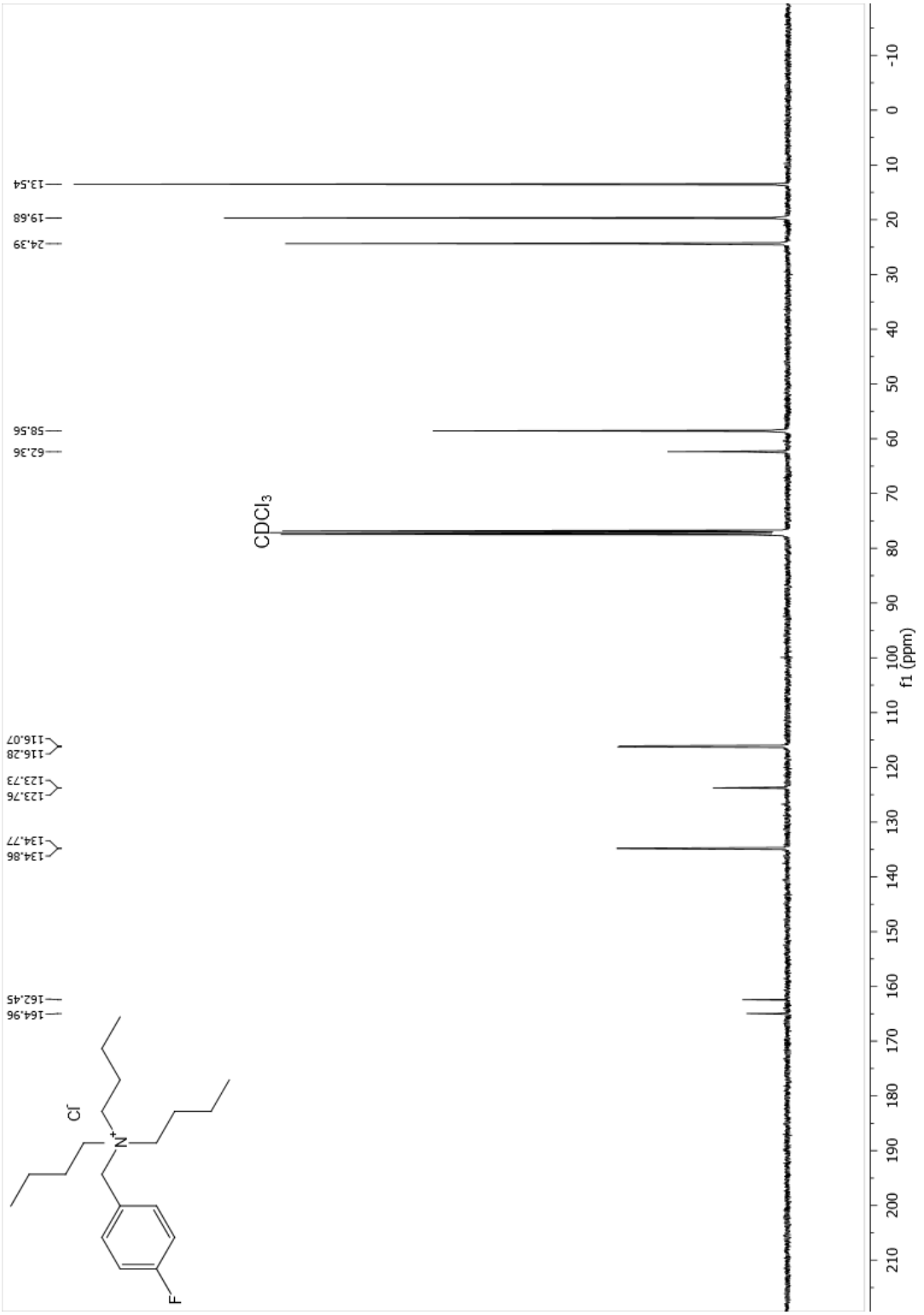
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7d (*N*,*N*-dibutyl-*N*-(4-fluorobenzyl)butan-1-aminium chloride)



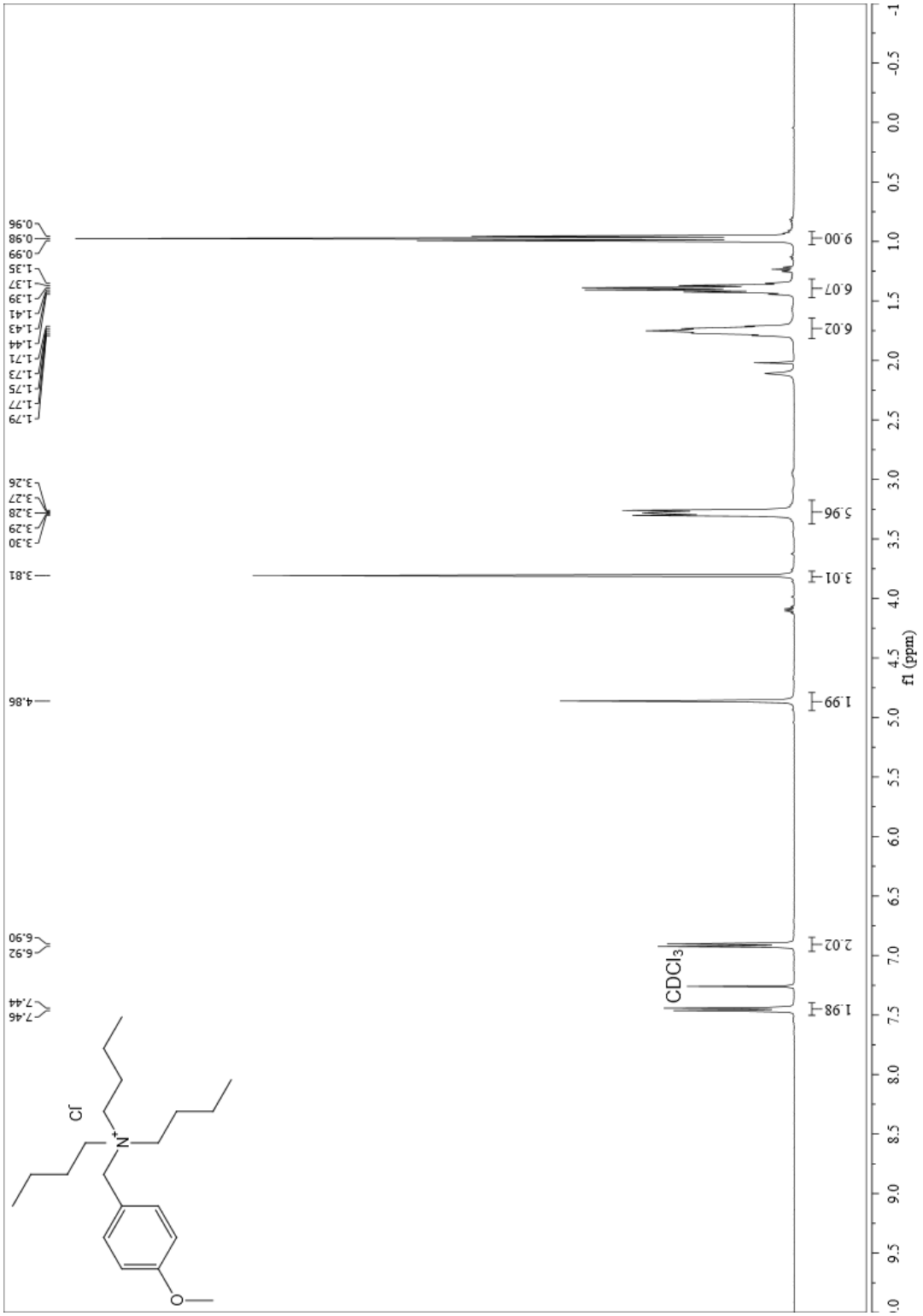
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7d (*N,N*-dibutyl-*N*-(4-fluorobenzyl)butan-1-aminium chloride*)*



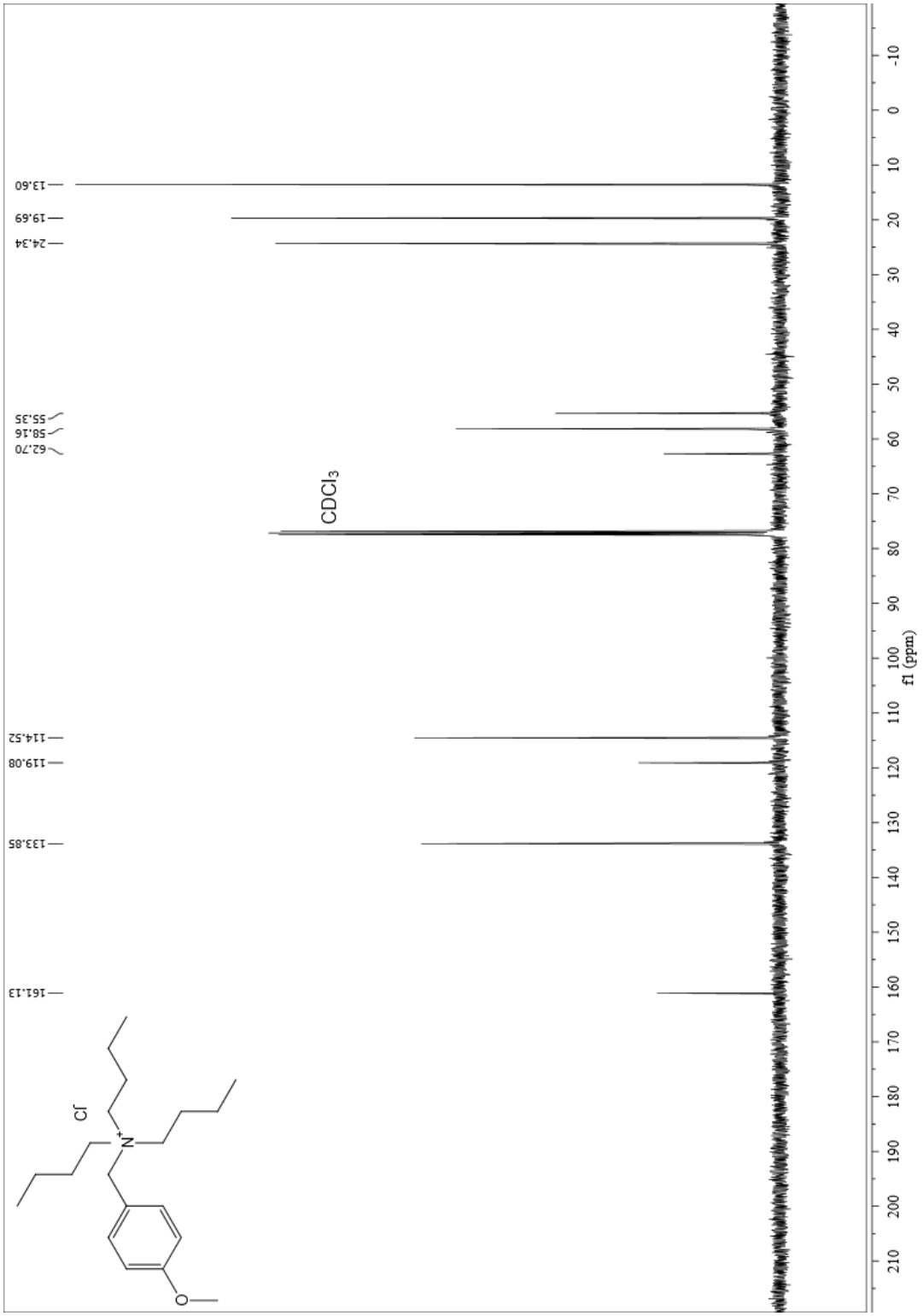
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7d (*N*,*N*-dibutyl-*N*-(4-fluorobenzyl)butan-1-aminium chloride)



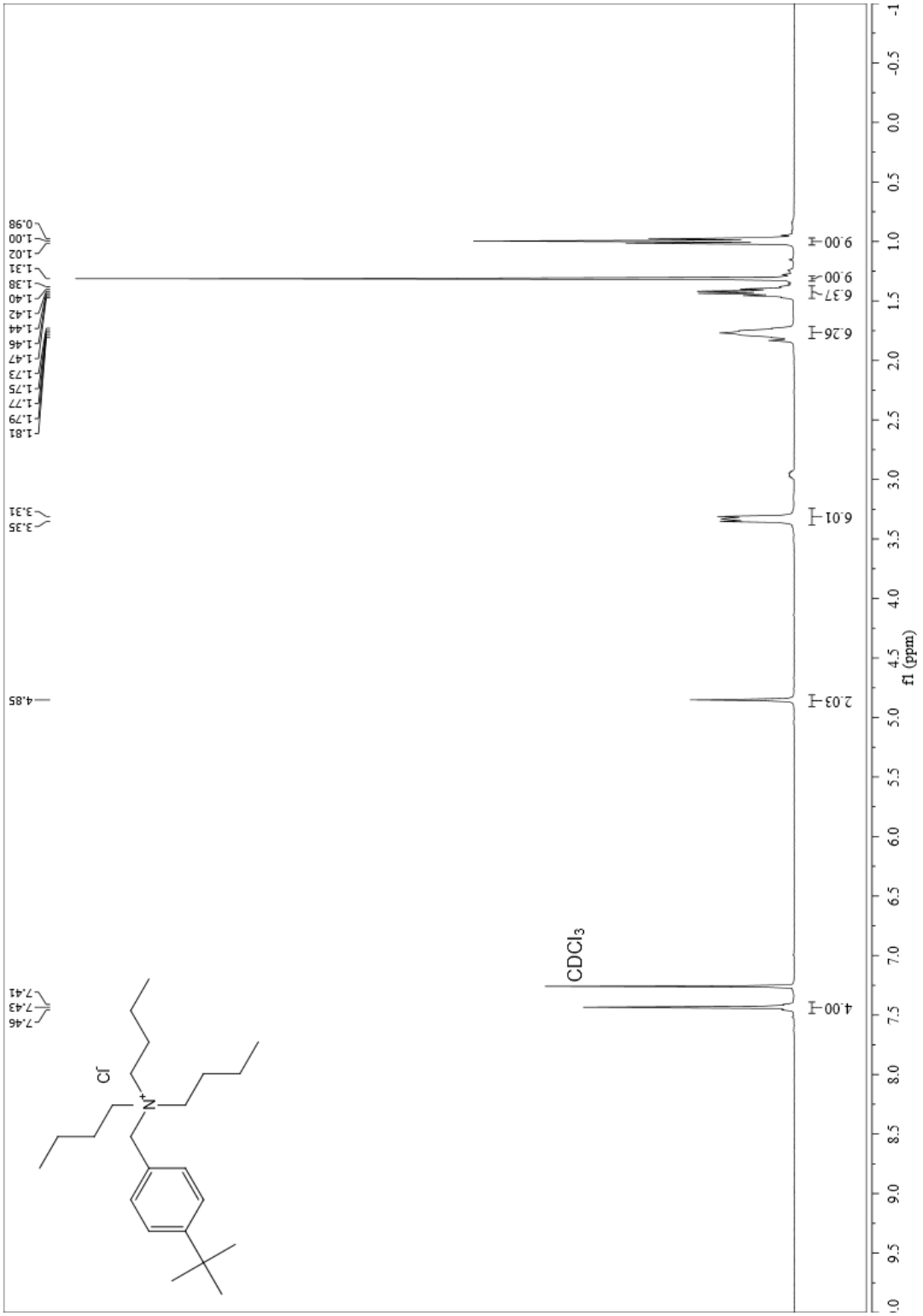
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7e (*N*,*N*-dibutyl-*N*-(4-methoxybenzyl)butan-1-aminium chloride)



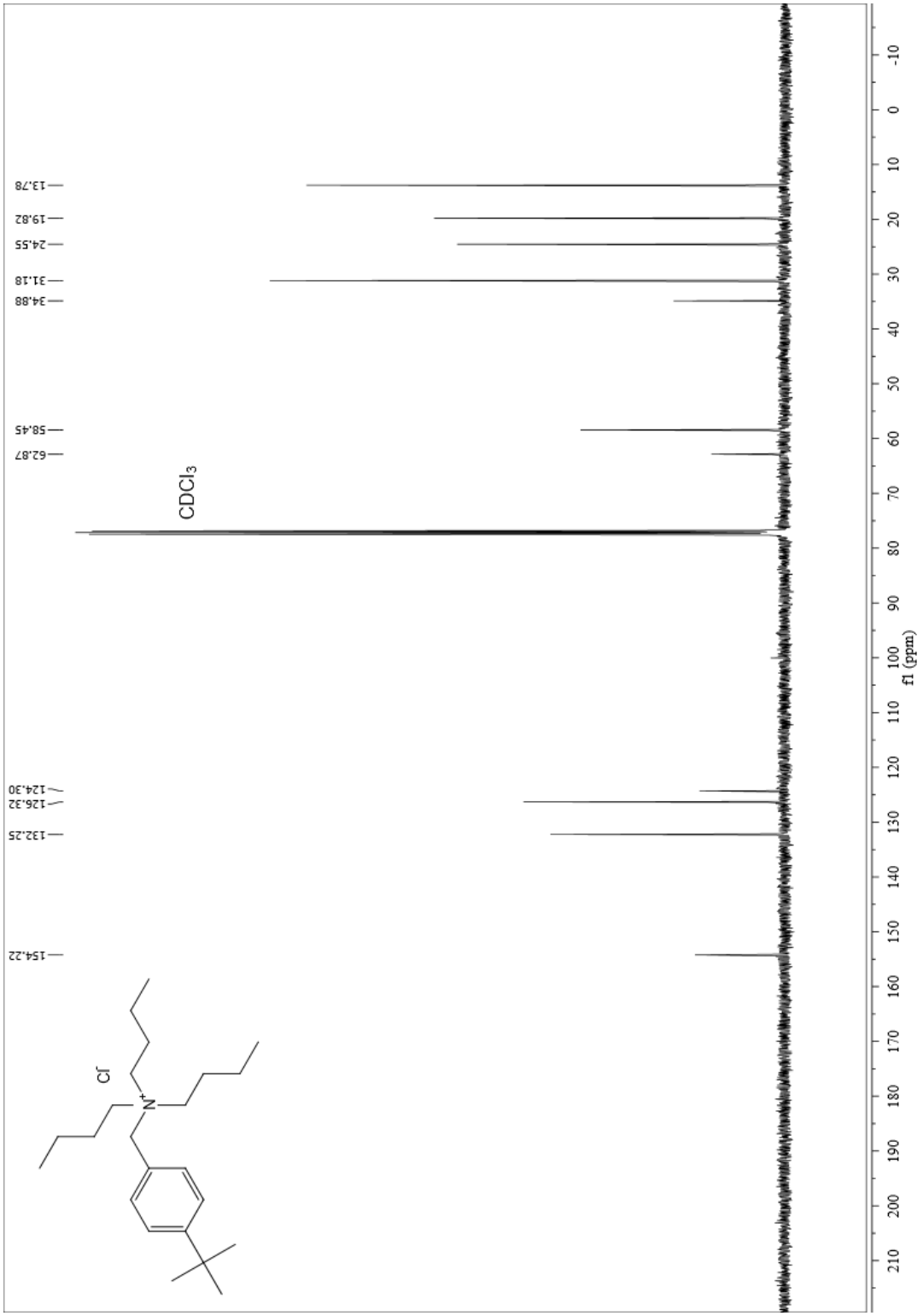
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7e (*N*,*N*-dibutyl-*N*-(4-methoxybenzyl)butan-1-aminium chloride)



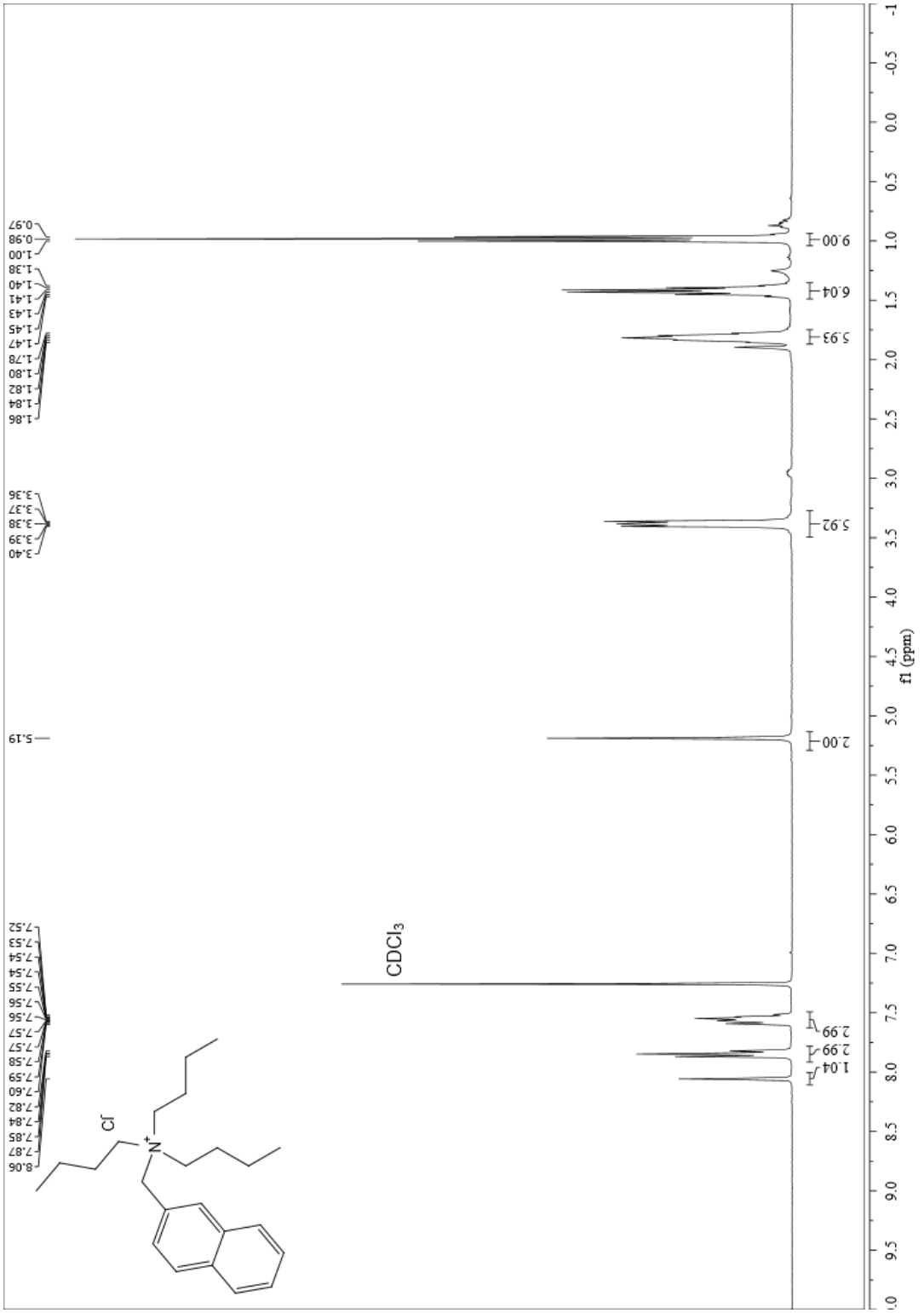
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7f (*N*,*N*-dibutyl-*N*-(4-(tert-butyl)benzyl)butan-1-aminium chloride)



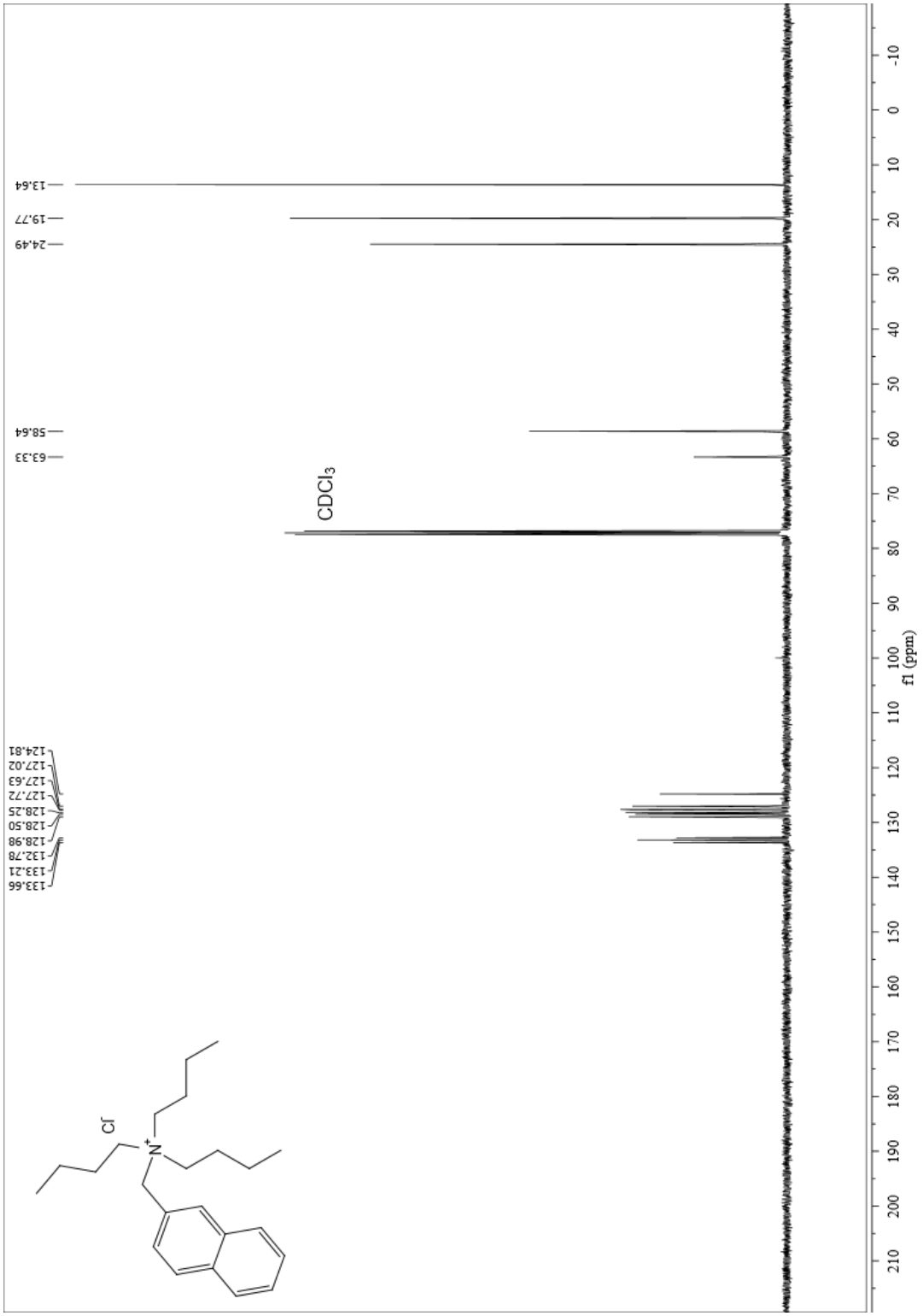
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7f (*N*,*N*-dibutyl-*N*-(4-(tert-butyl)benzyl)butan-1-aminium chloride)



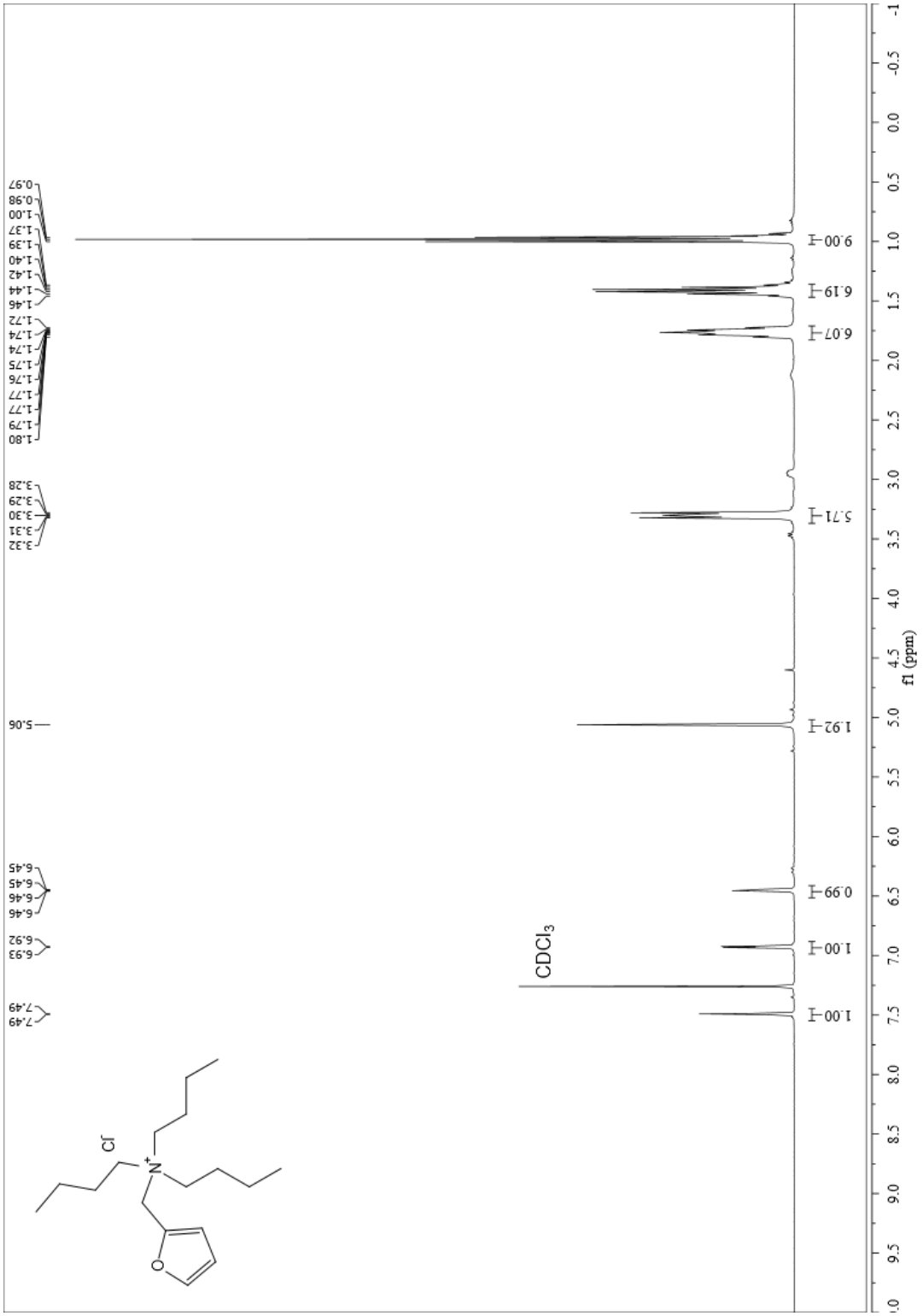
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7h (*N*,*N*-dibutyl-*N*-(naphthalen-2-ylmethyl)butan-1-aminium chloride)



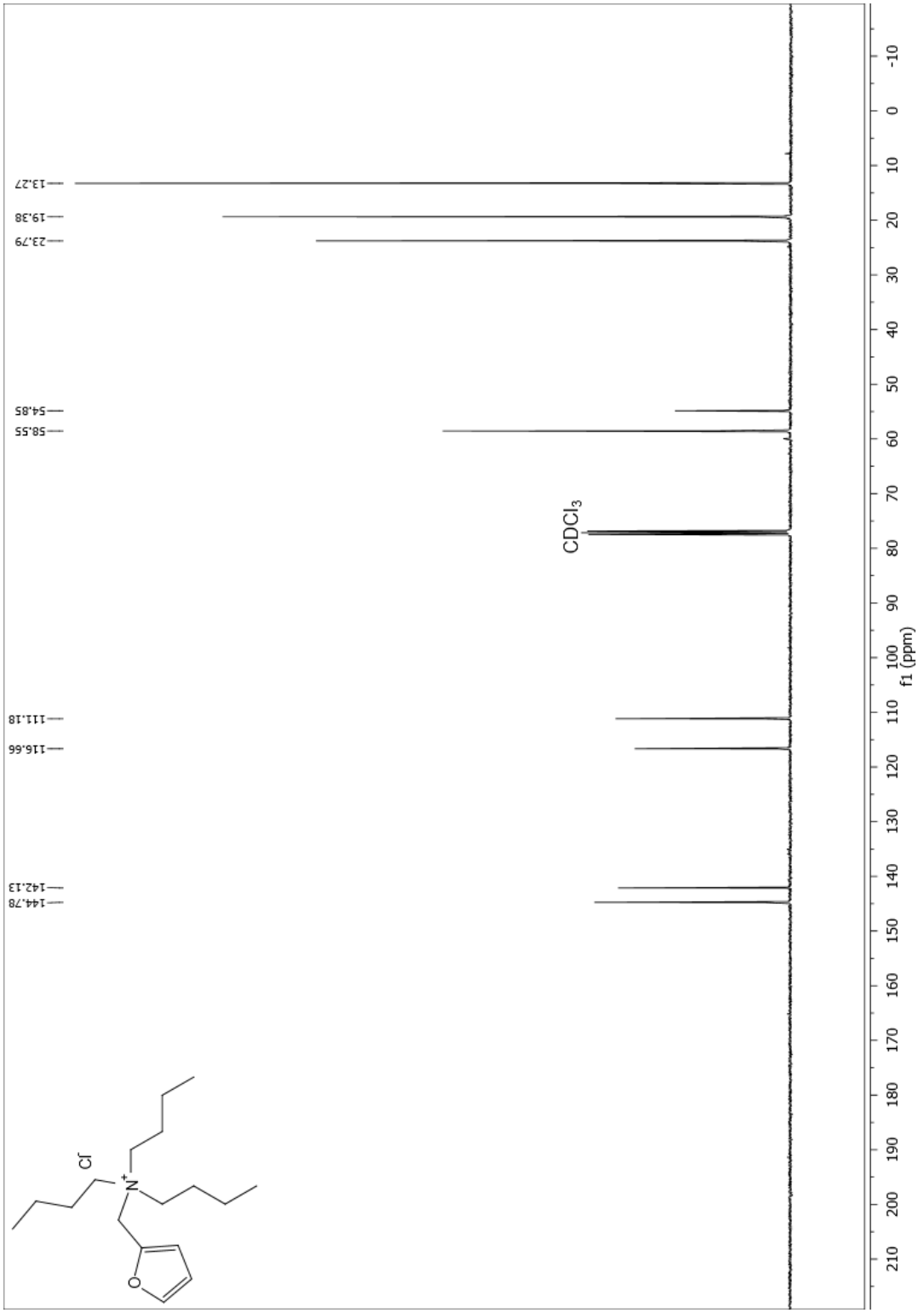
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7h (*N*,*N*-dibutyl-*N*-(naphthalen-2-ylmethyl)butan-1-aminium chloride)



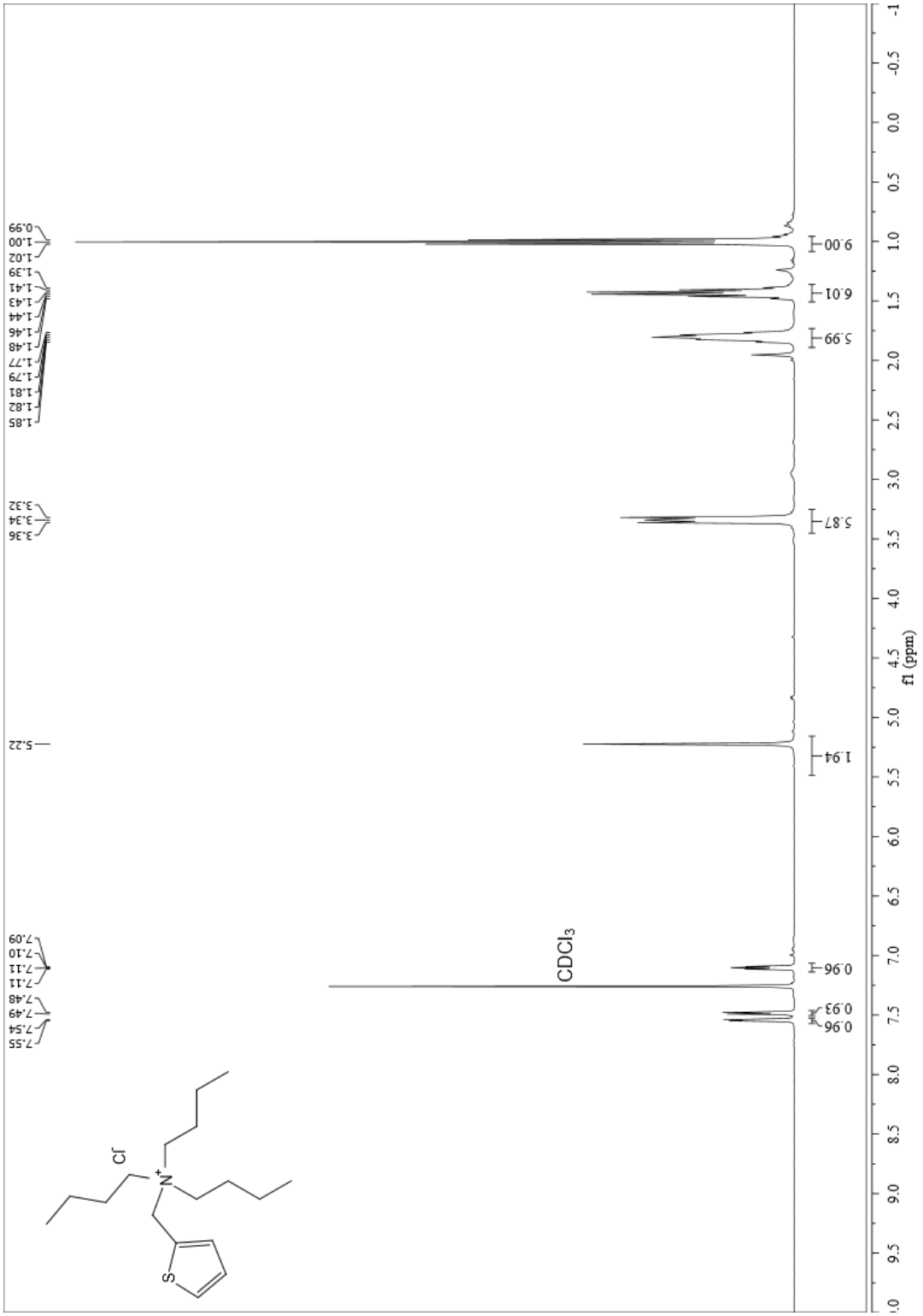
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7i (*N,N*-dibutyl-*N*-(furan-2-ylmethyl)butan-1-aminium chloride)



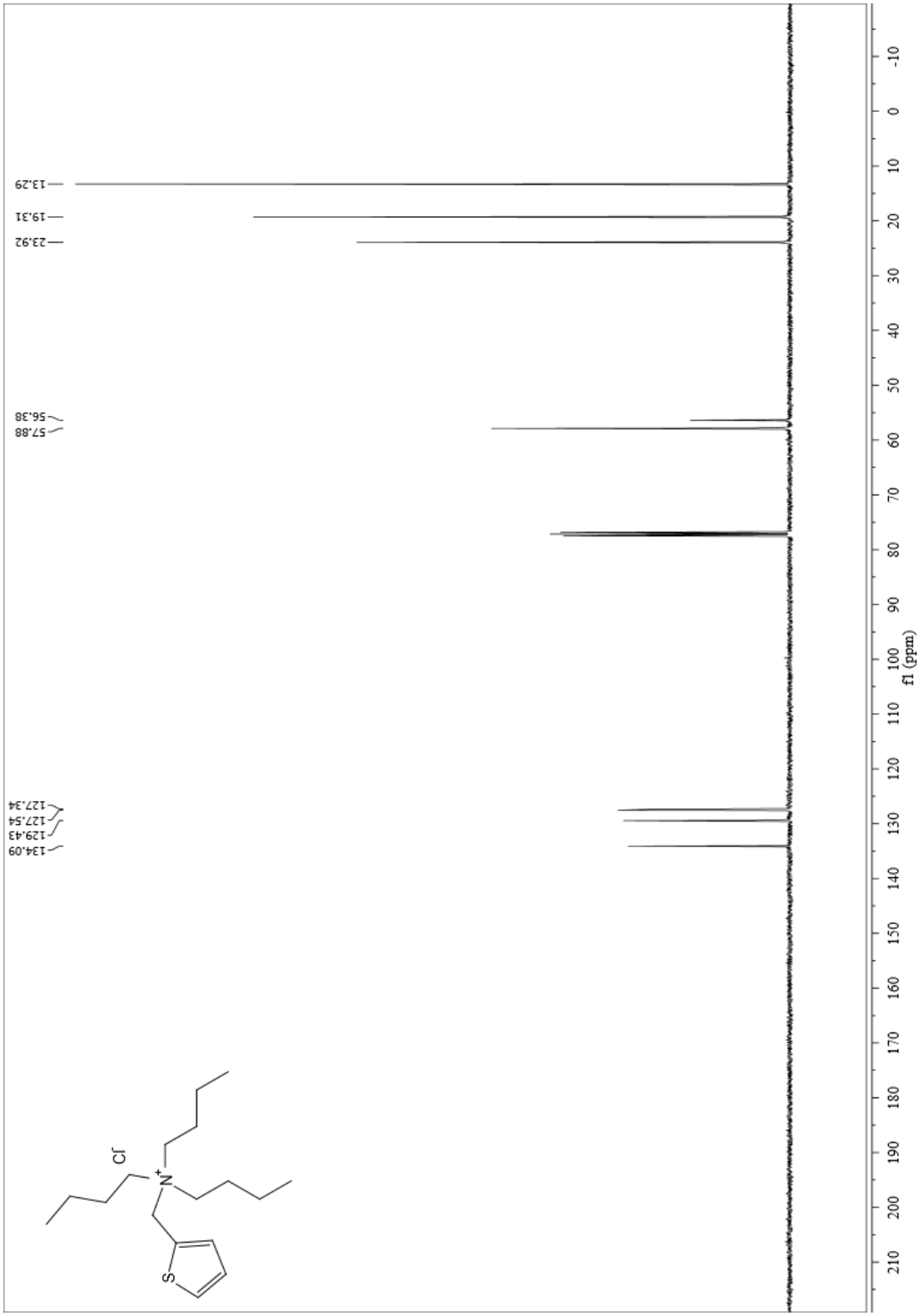
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7i (*N*,*N*-dibutyl-*N*-(furan-2-ylmethyl)butan-1-aminium chloride)



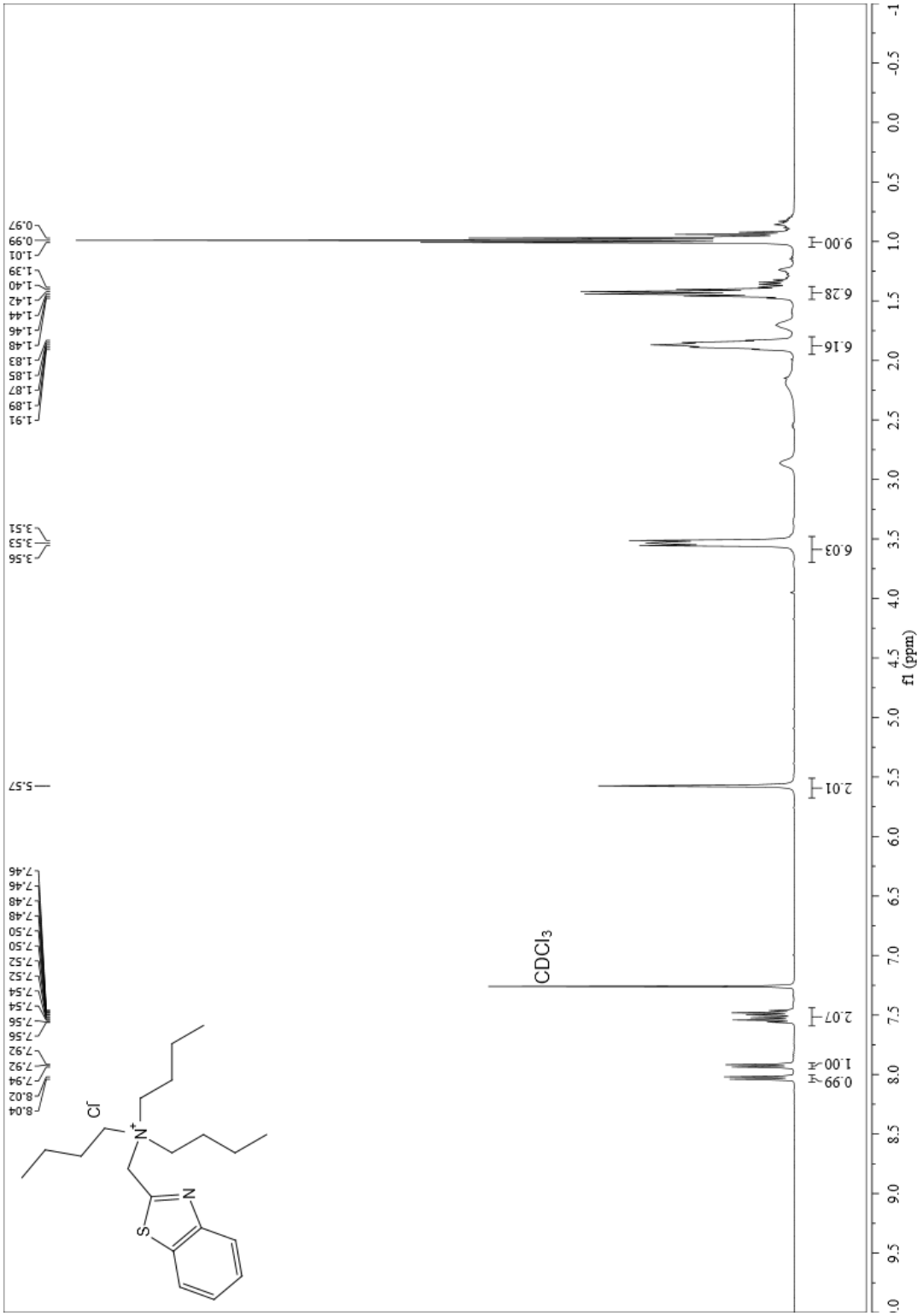
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7j (*N*,*N*-dibutyl-*N*-(thiophen-2-ylmethyl)butan-1-aminium chloride)



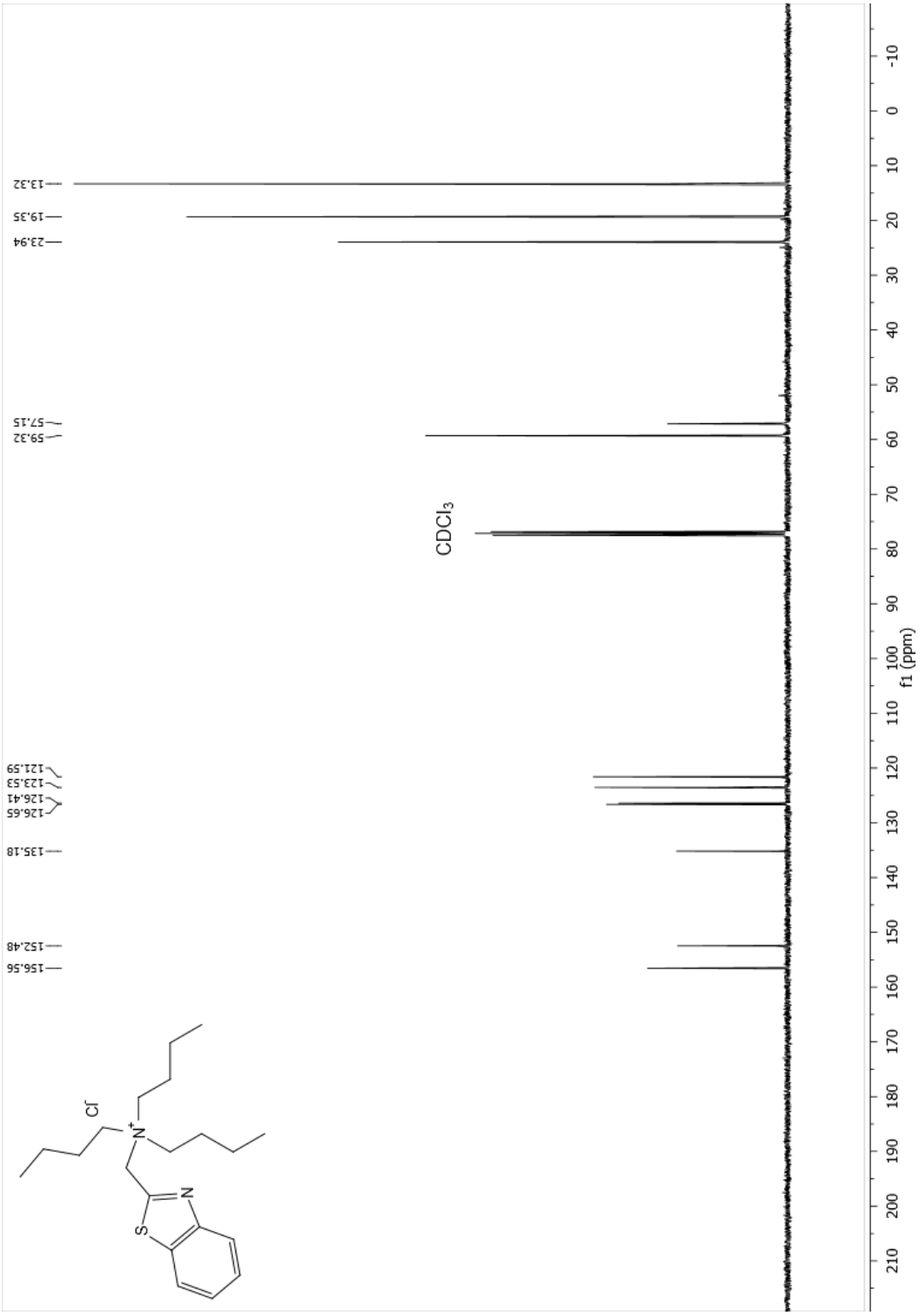
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7j (*N*,*N*-dibutyl-*N*-(thiophen-2-ylmethyl)butan-1-aminium chloride)



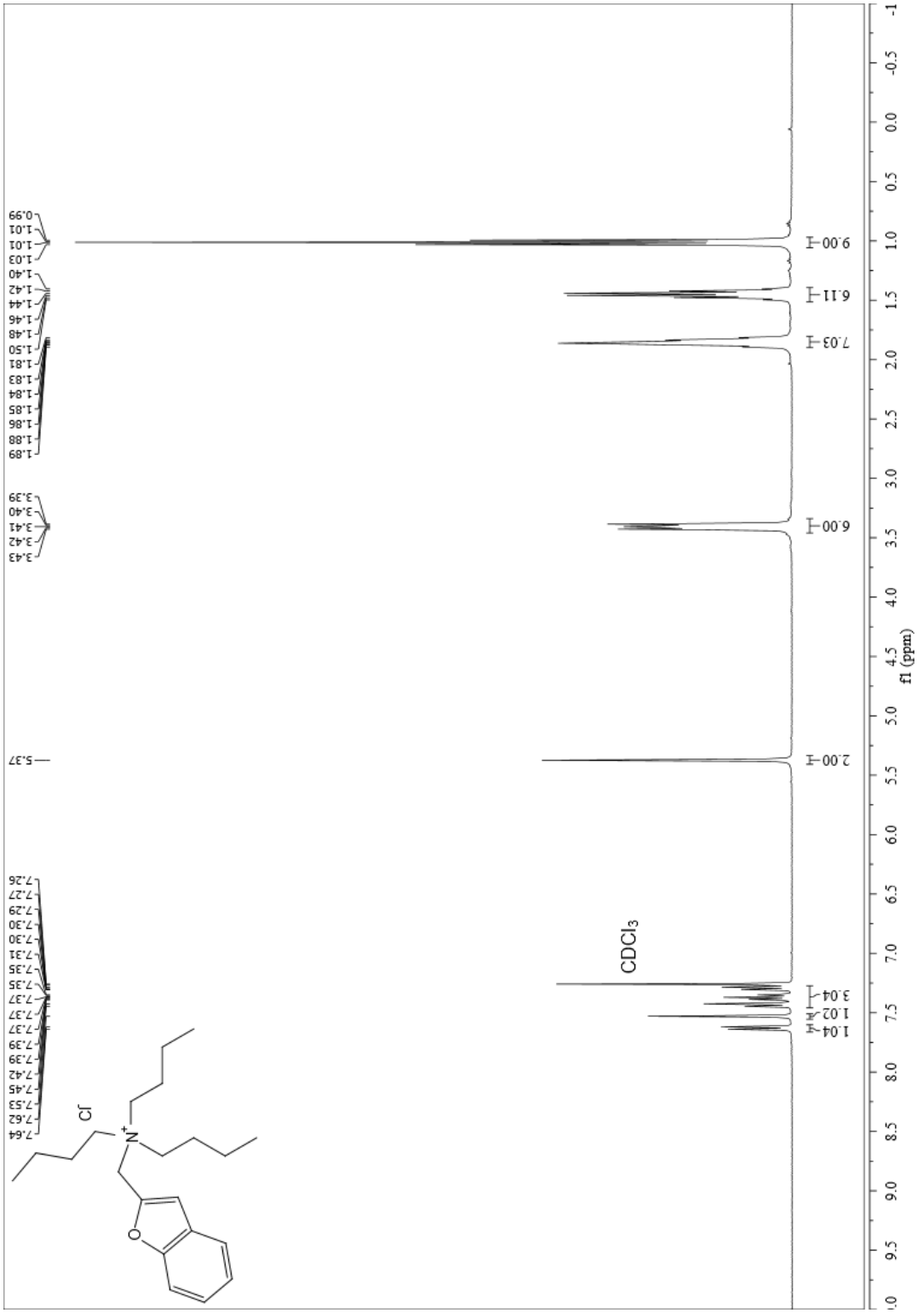
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7k (*N*-(benzo[*d*]thiazol-2-ylmethyl)-*N*,*N*-dibutylbutan-1-aminium chloride)



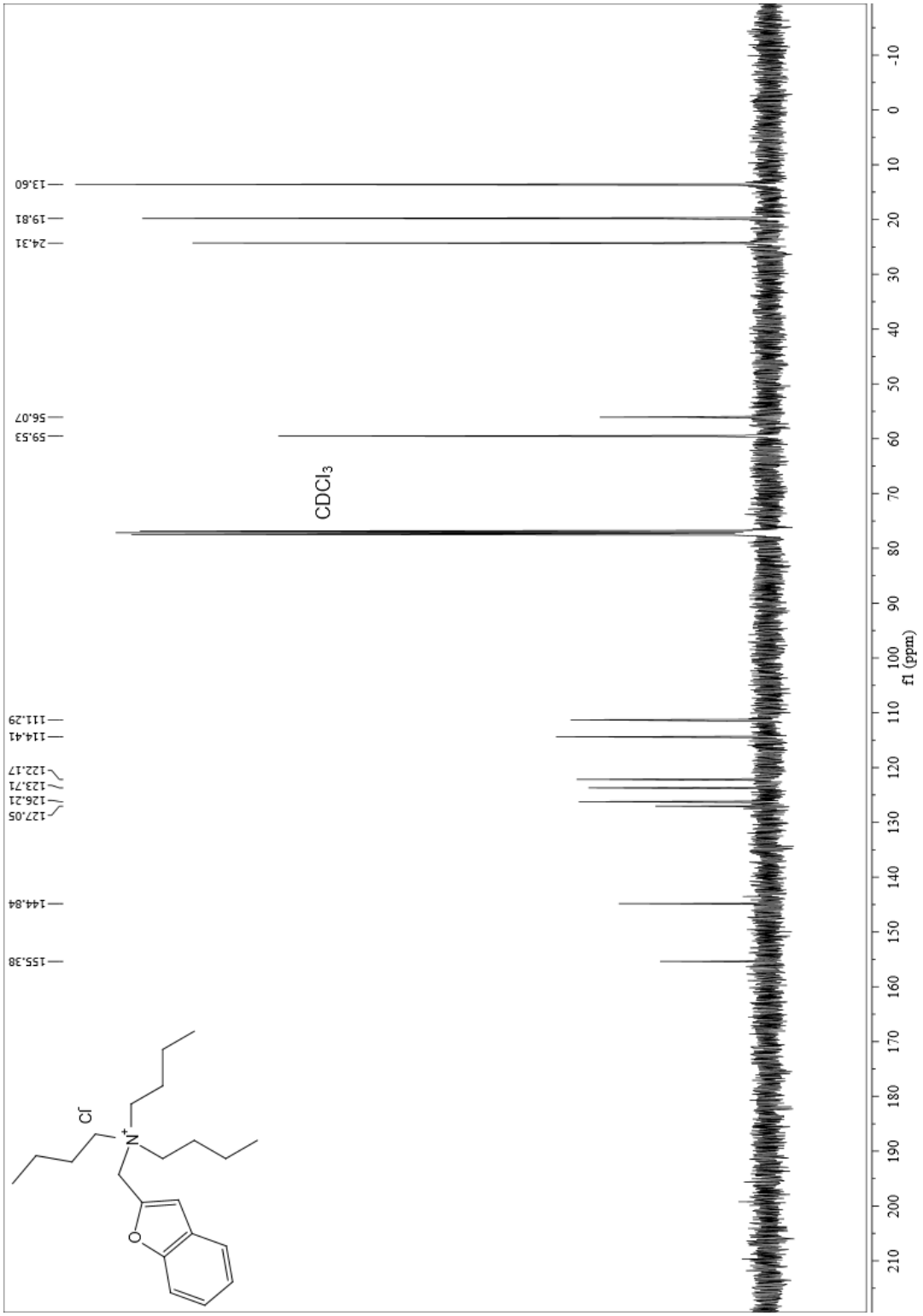
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7k (*N*-(benzo[*d*]thiazol-2-ylmethyl)-*N*,*N*-dibutylbutan-1-aminium chloride)



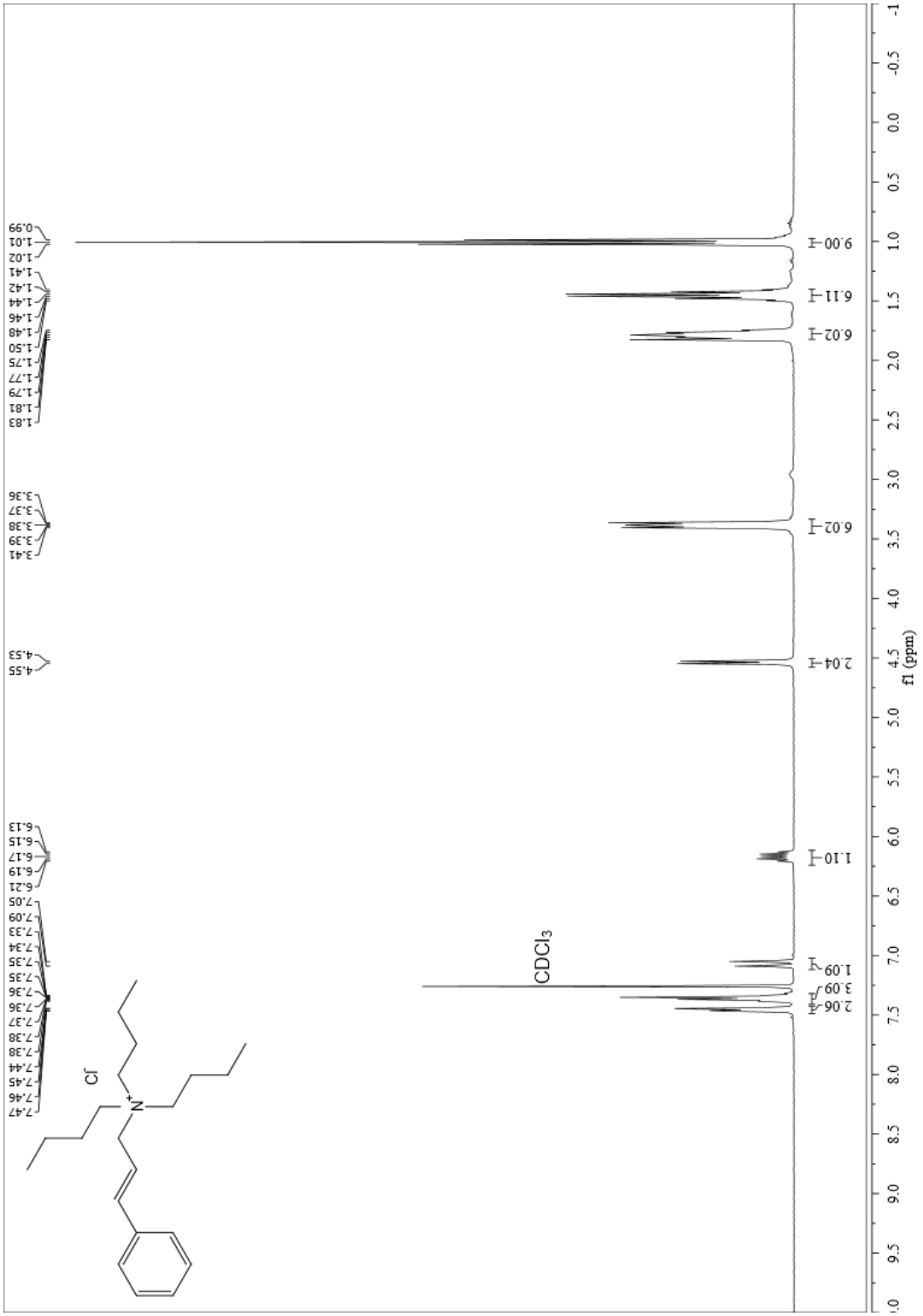
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7l (*N*-(benzofuran-2-ylmethyl)-*N*,*N*-dibutylbutan-1-aminium chloride)



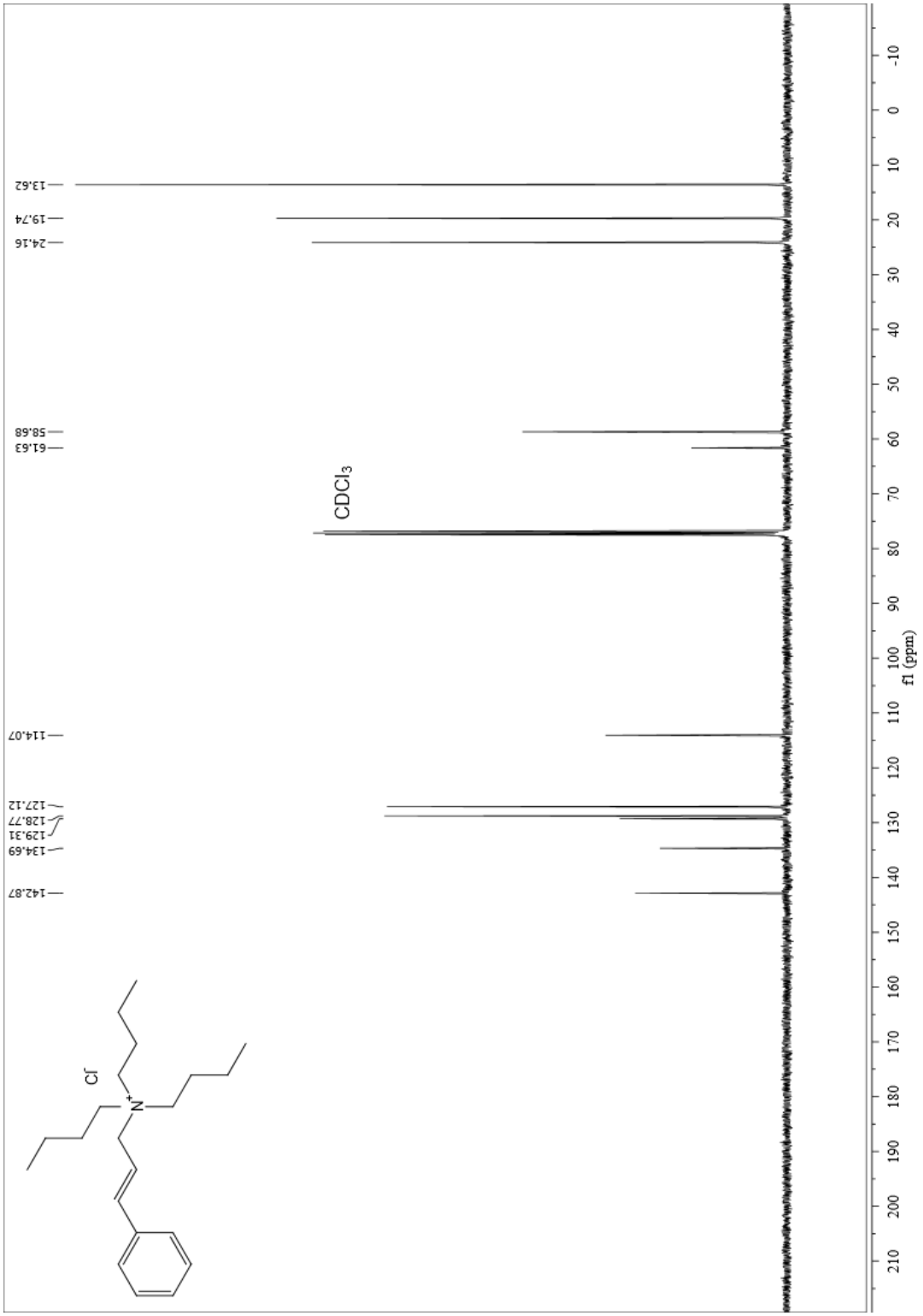
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7l (*N*-(benzofuran-2-ylmethyl)-*N*,*N*-dibutylbutan-1-aminium chloride)



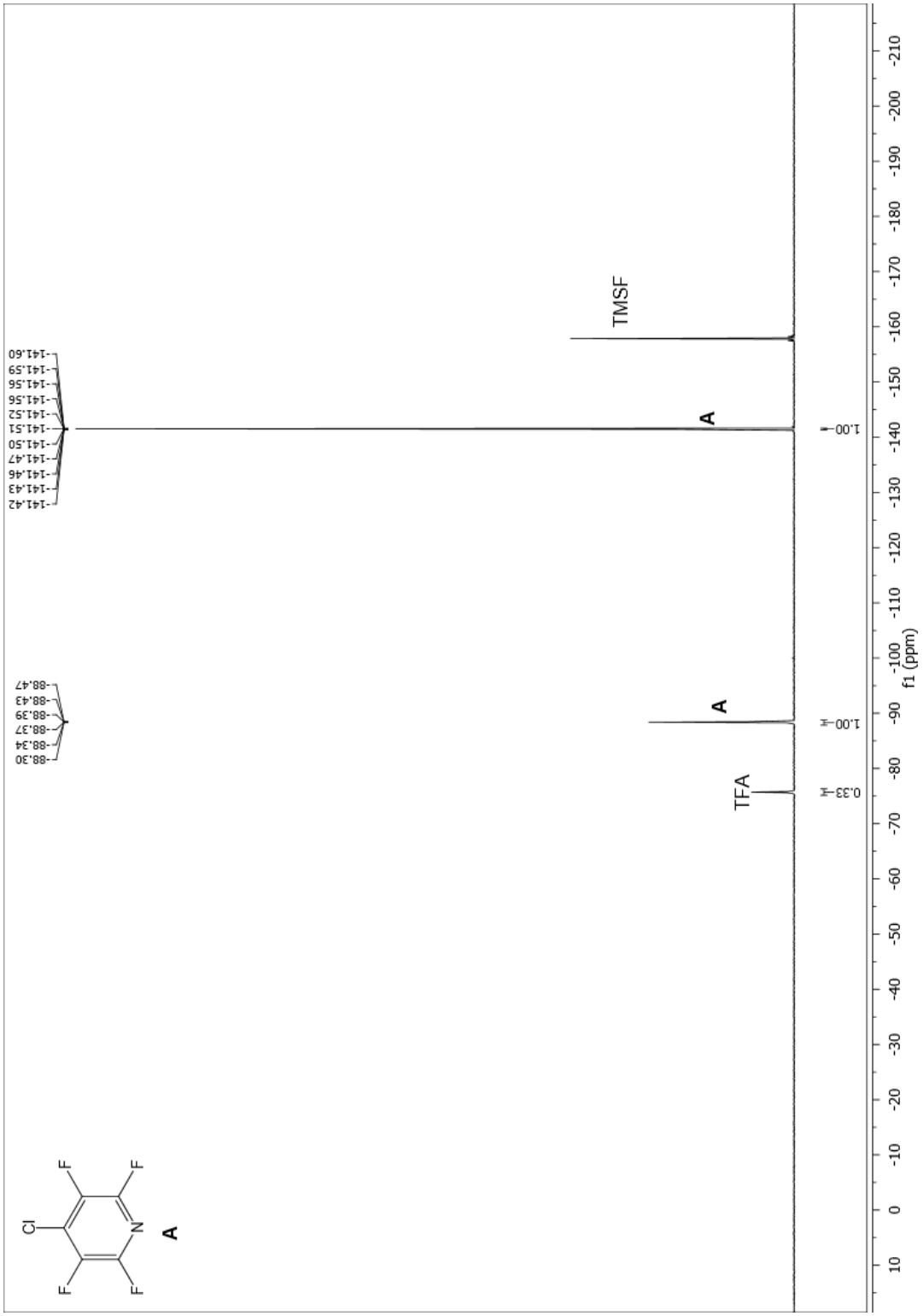
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7m (*N*,*N*-dibutyl-*N*-cinnamylbutan-1-aminium chloride)



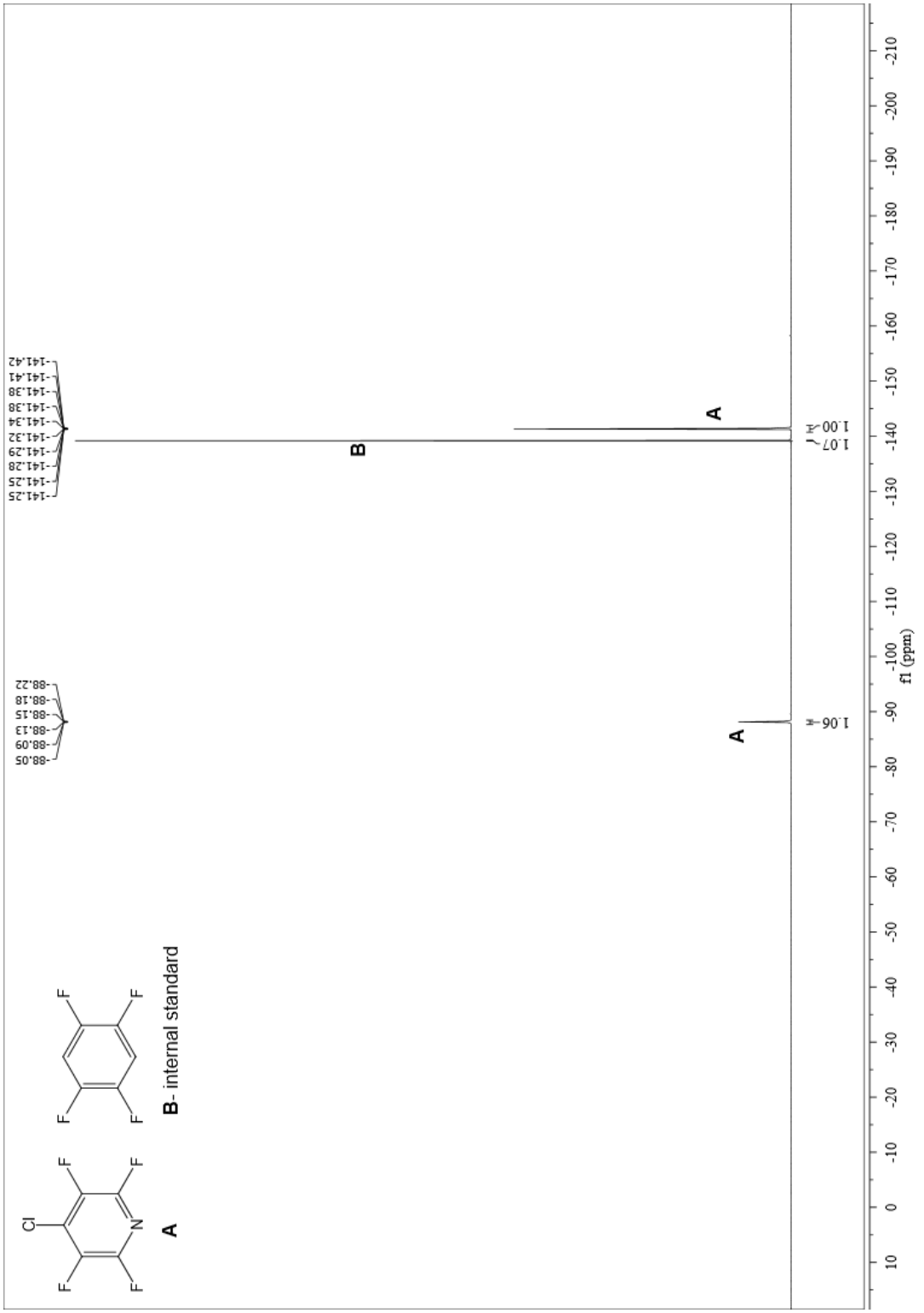
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 5.7m (*N*,*N*-dibutyl-*N*-cinnamylbutan-1-aminium chloride)



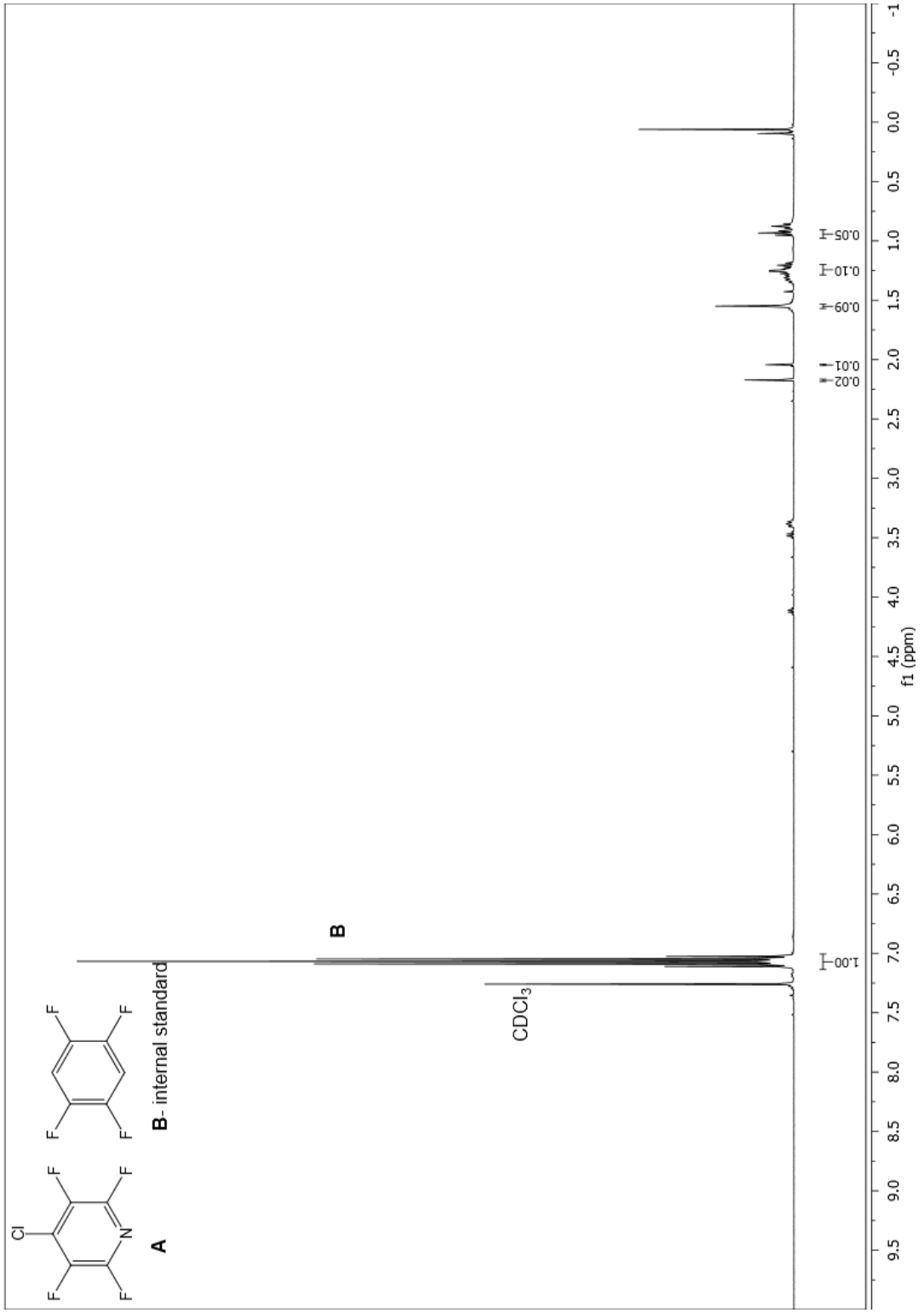
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of crude 4-chloro-2,3,5,6-tetrafluoropyridine (5.9a) for NMR yield calculation



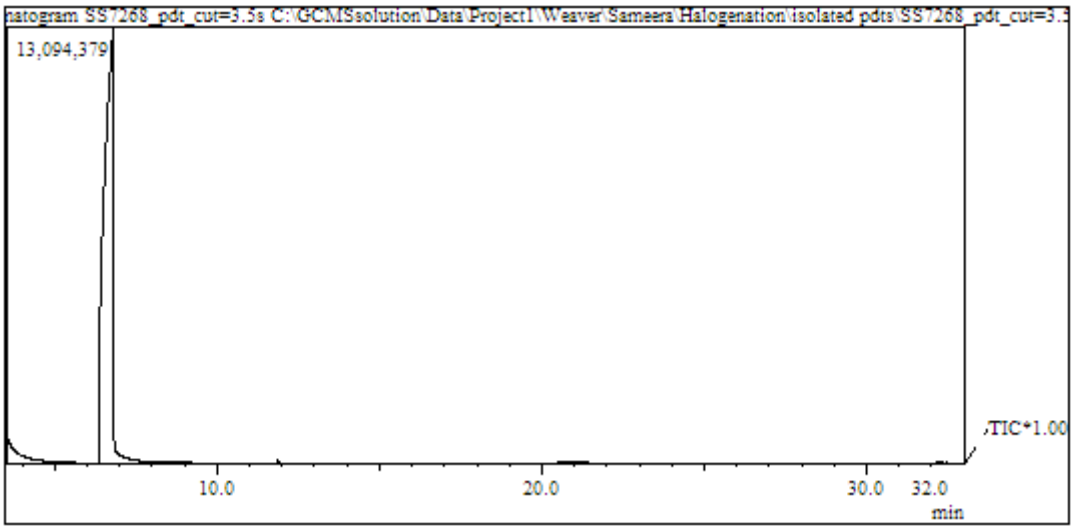
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 4-chloro-2,3,5,6-tetrafluoropyridine (5.9a) with 1,2,4,5-tetrafluorobenzene as an internal standard

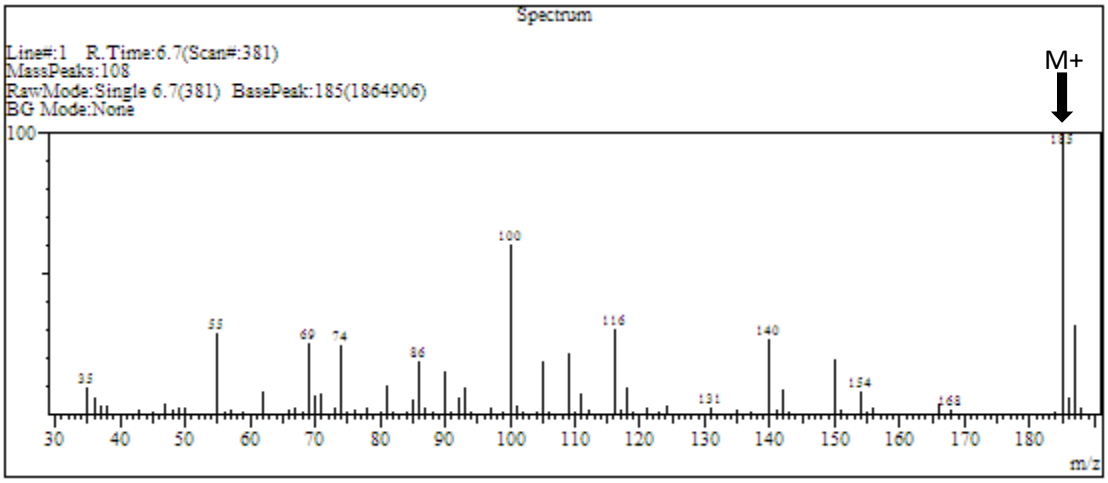


^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of crude 4-chloro-2,3,5,6-tetrafluoropyridine (5.9a) with 1,2,4,5-tetrafluorobenzene as an internal standard

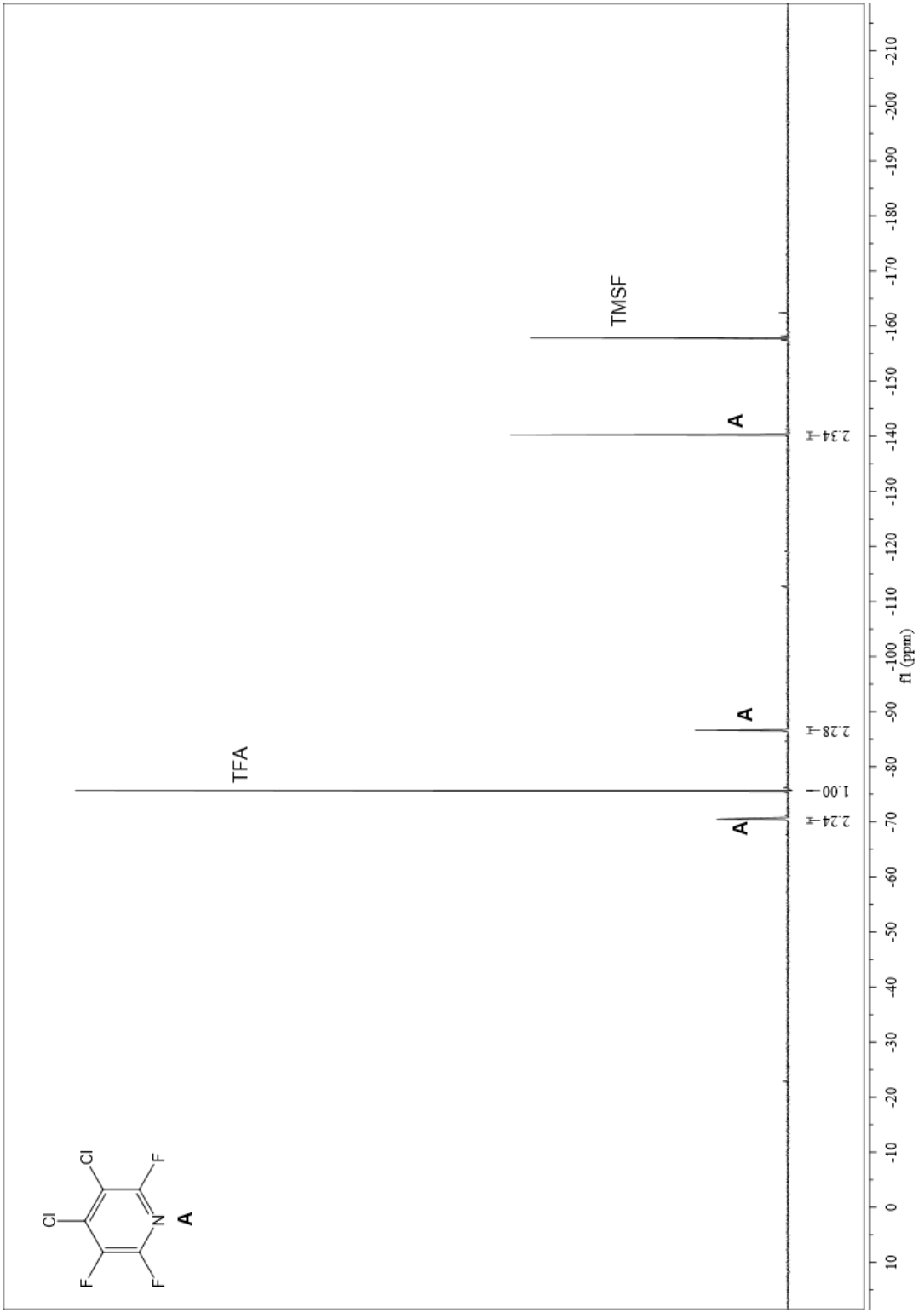


GC and MS of 4-chloro-2,3,5,6-tetrafluoropyridine (5.9a)

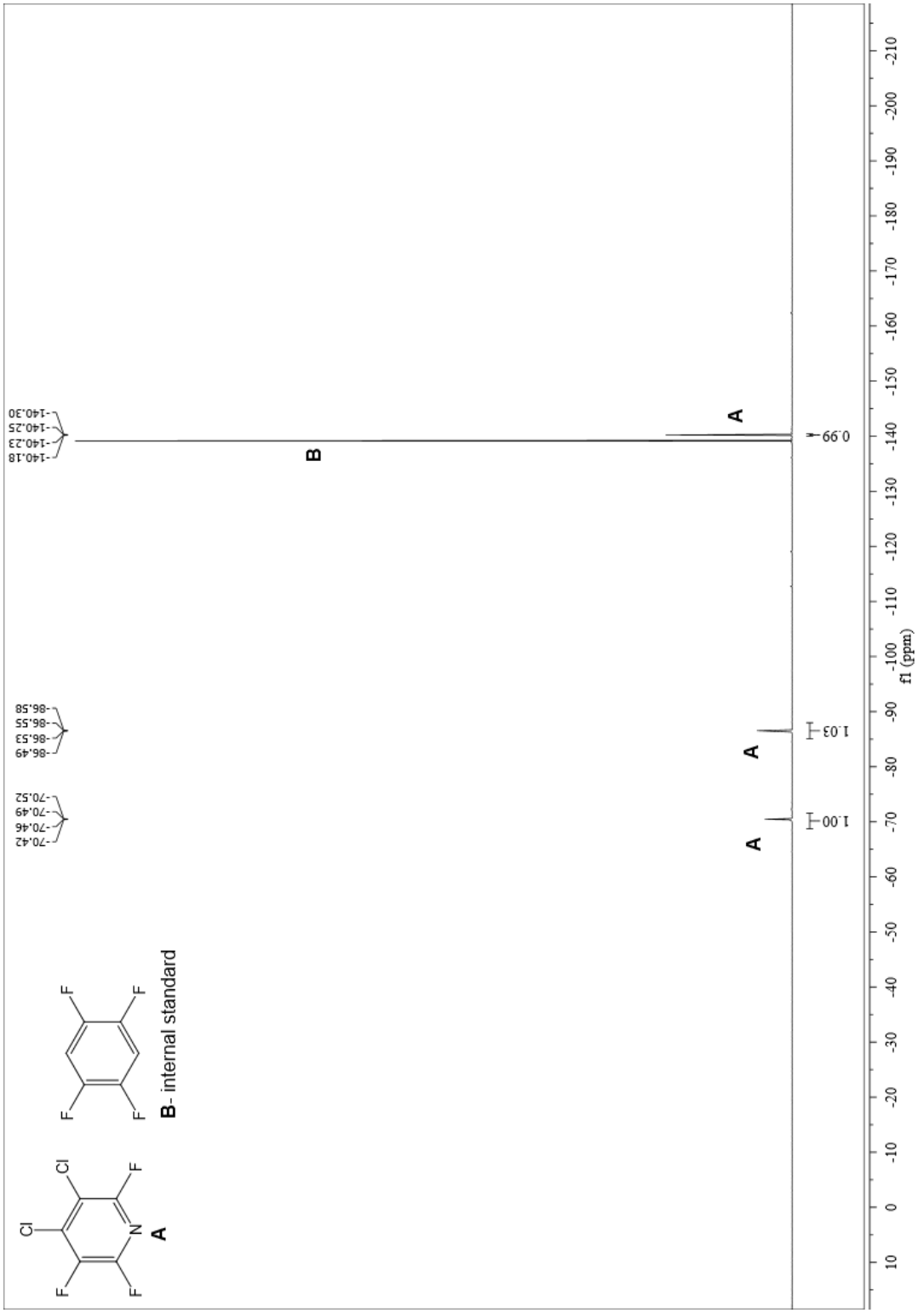




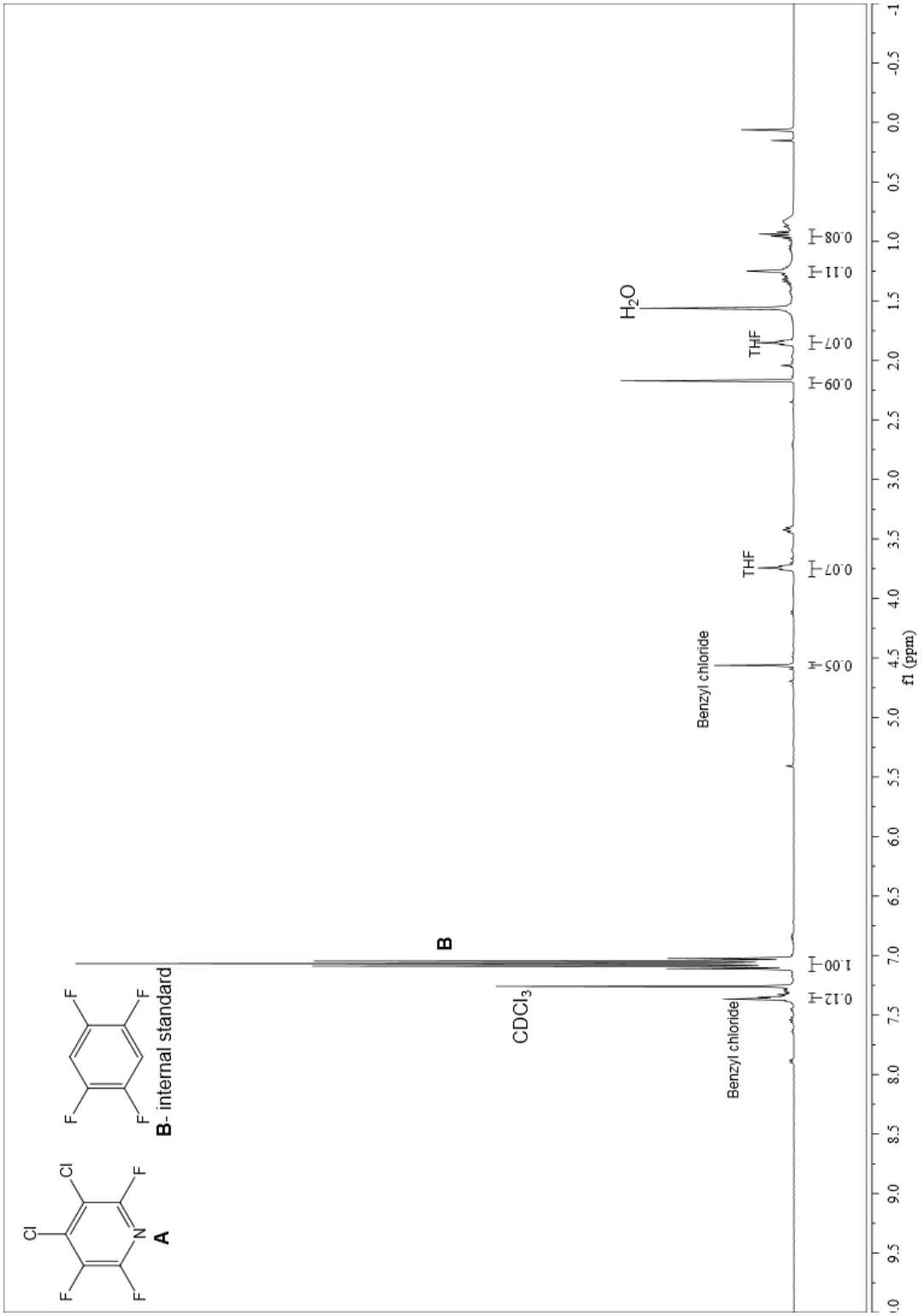
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of crude 3,4-dichloro-2,5,6-trifluoropyridine (5.9b) for NMR yield calculation



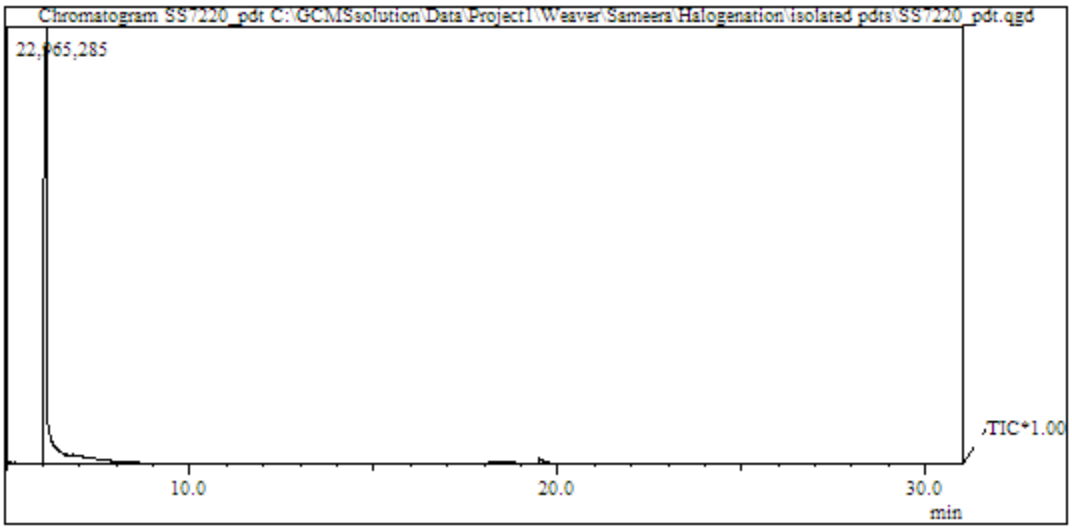
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 3,4-dichloro-2,5,6-trifluoropyridine (5.9b) with 1,2,4,5-tetrafluorobenzene as an internal standard

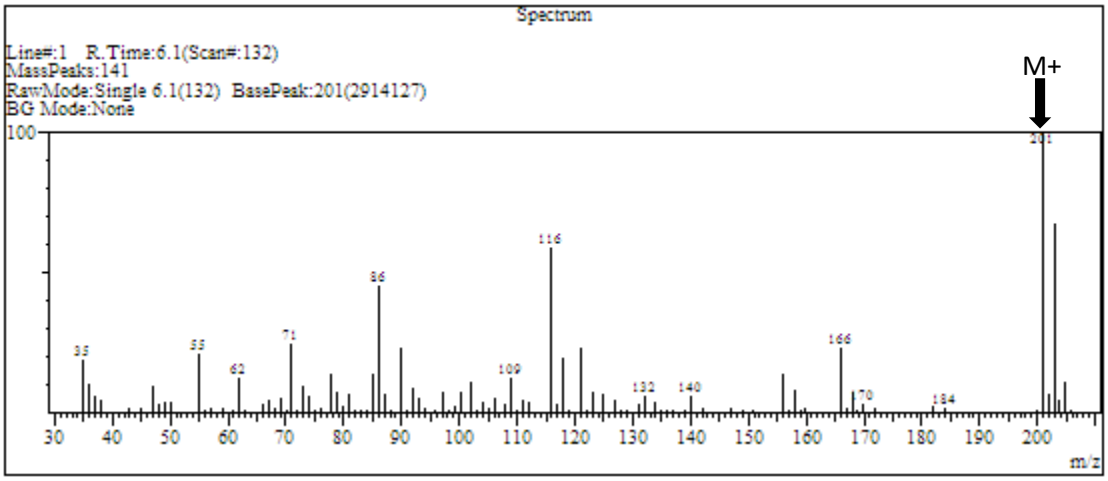


^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 3,4-dichloro-2,5,6-trifluoropyridine (5.9b) with 1,2,4,5-tetrafluorobenzene as an internal standard

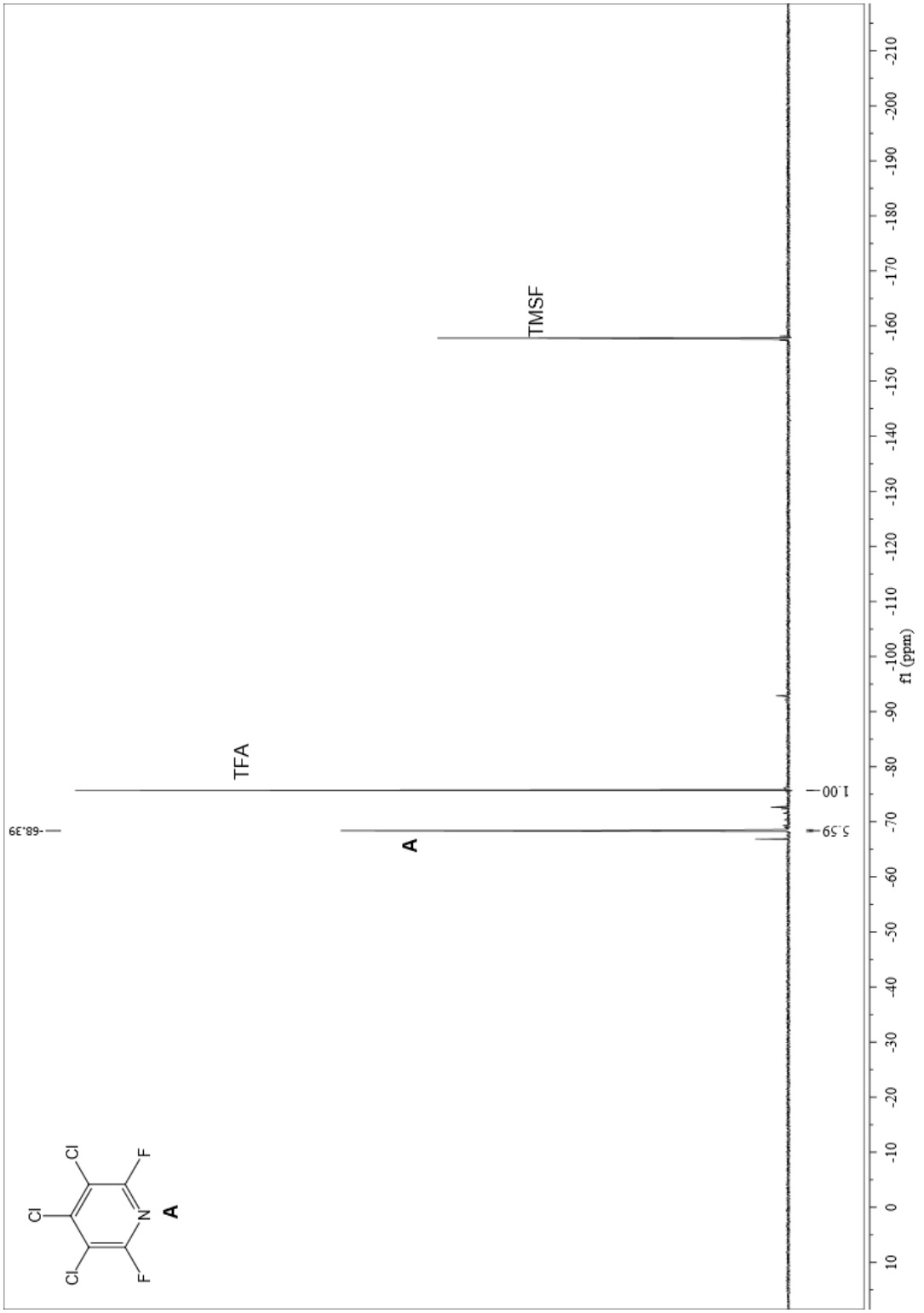


GC and MS of 3,4-dichloro-2,5,6-trifluoropyridine (5.9b)

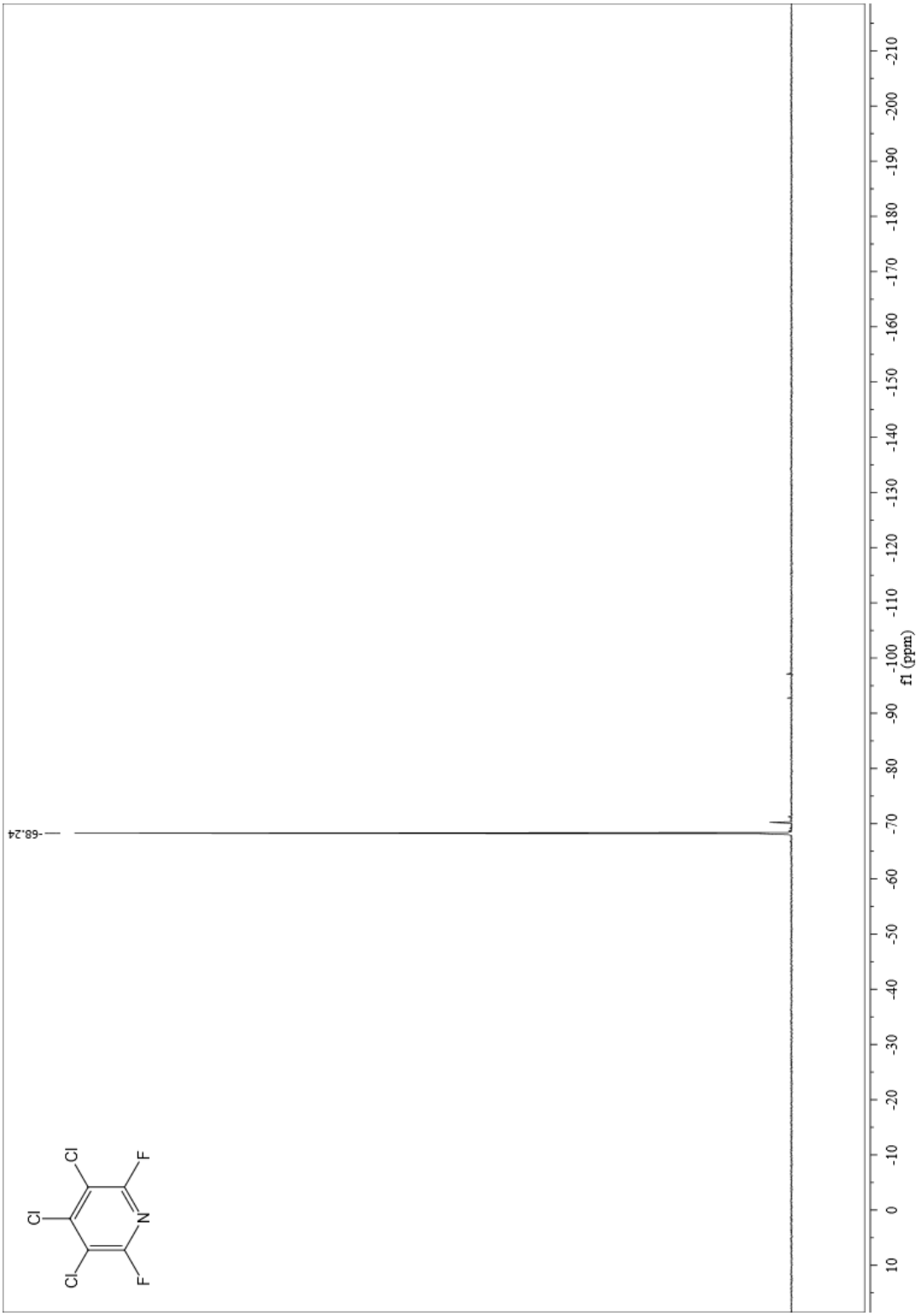




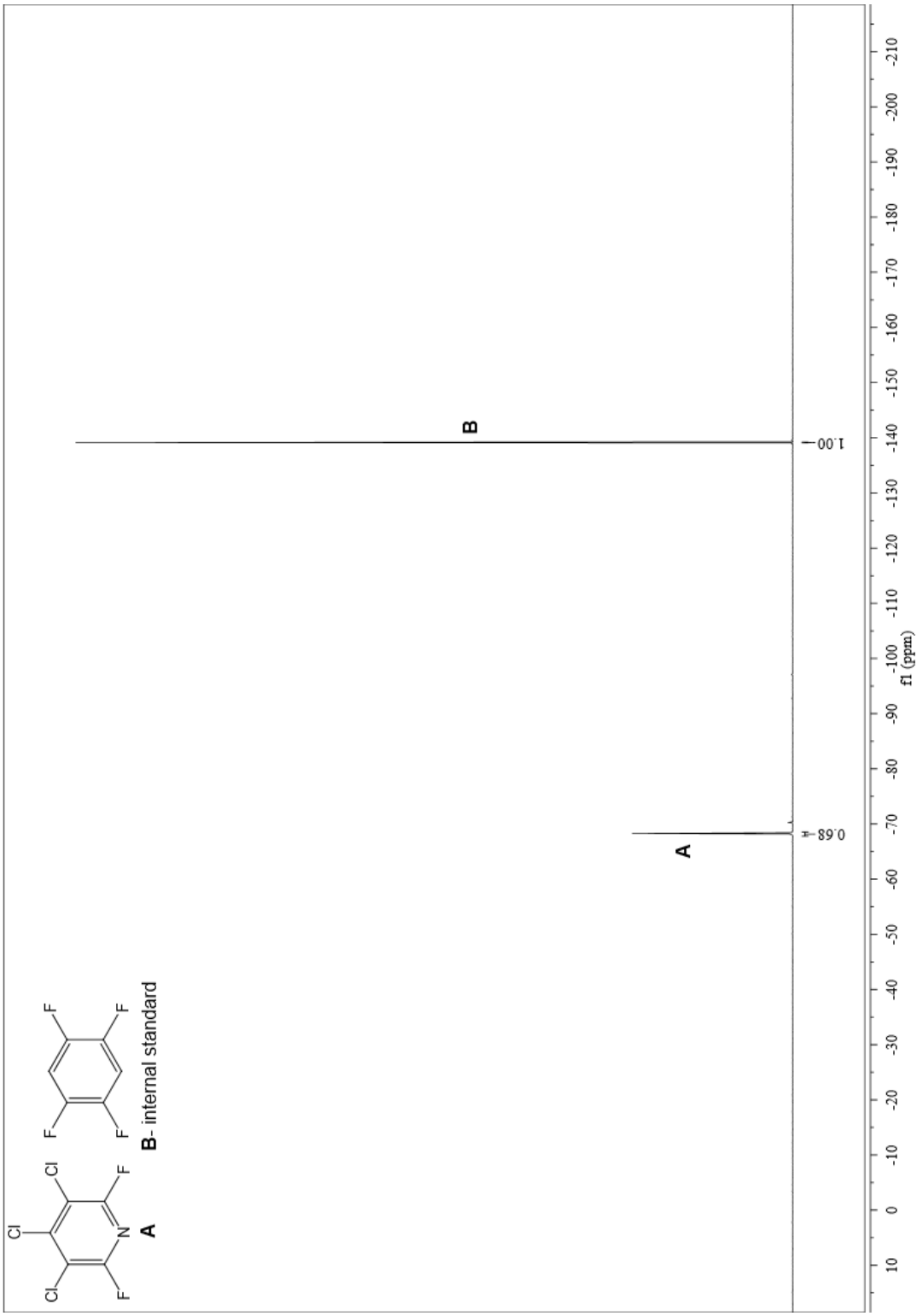
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of crude 3,4,5-trichloro-2,6-difluoropyridine (5.9c) for NMR yield calculation



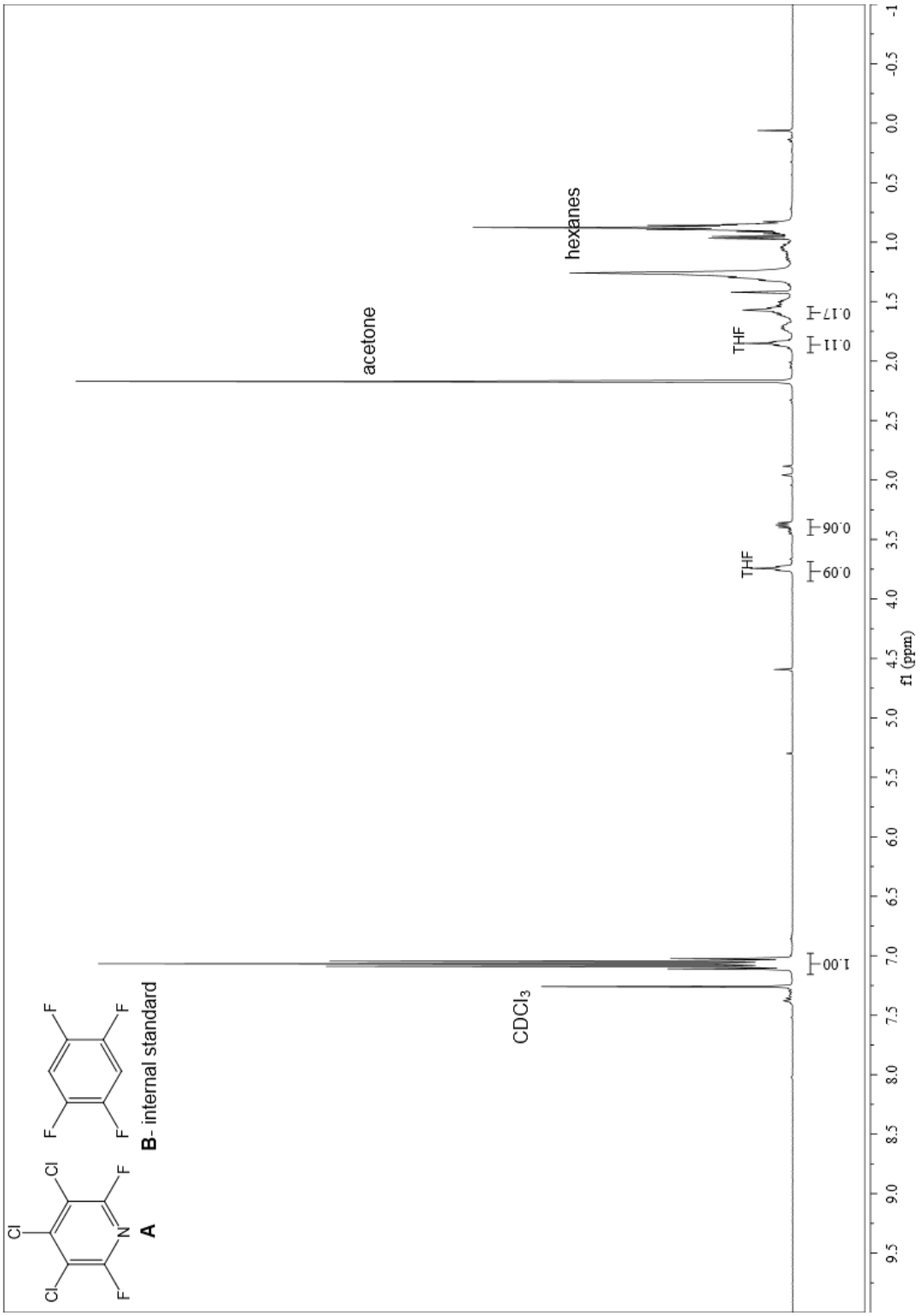
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 3,4,5-trichloro-2,6-difluoropyridine (5.9c)



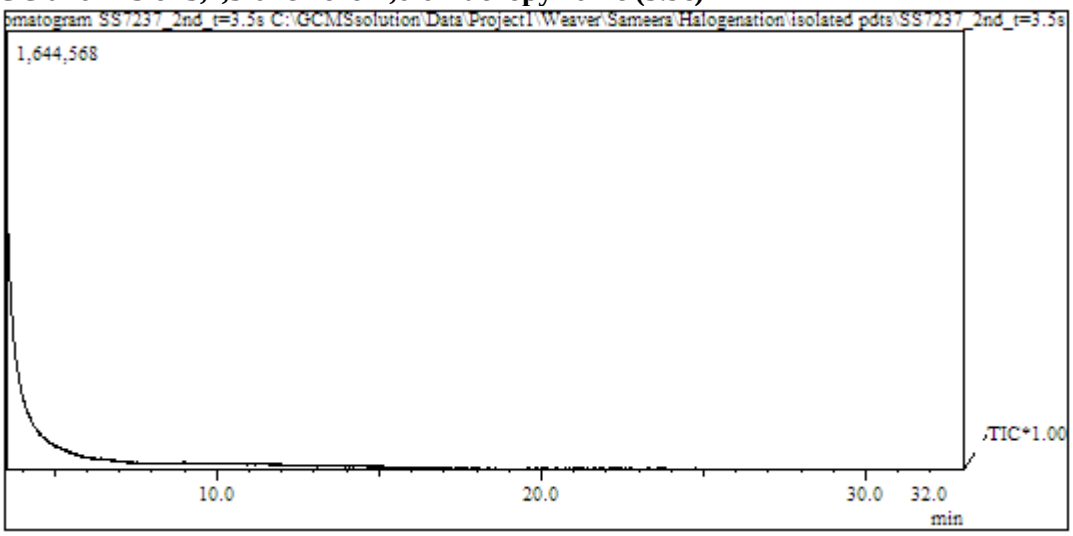
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 3,4,5-trichloro-2,6-difluoropyridine (5.9c) with 1,2,4,5-tetrafluorobenzene as an internal standard

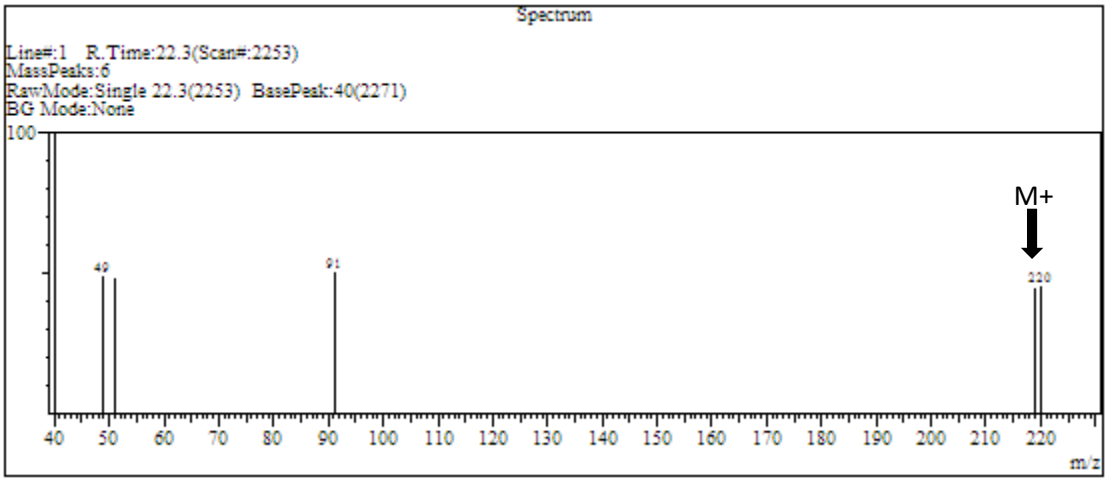


^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 3,4,5-trichloro-2,6-difluoropyridine (5.9c) with 1,2,4,5-tetrafluorobenzene as an internal standard

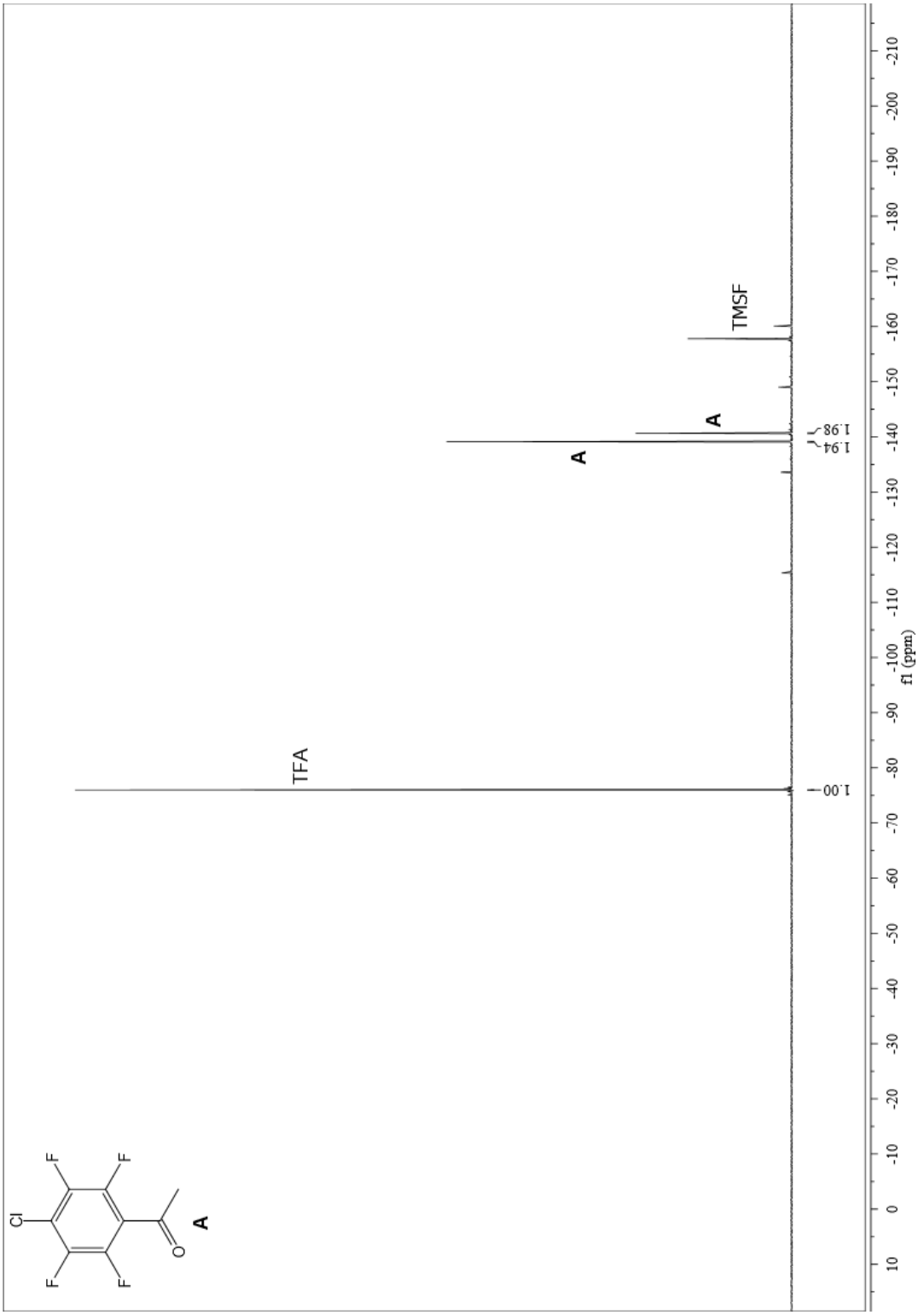


GC and MS of 3,4,5-trichloro-2,6-difluoropyridine (5.9c)

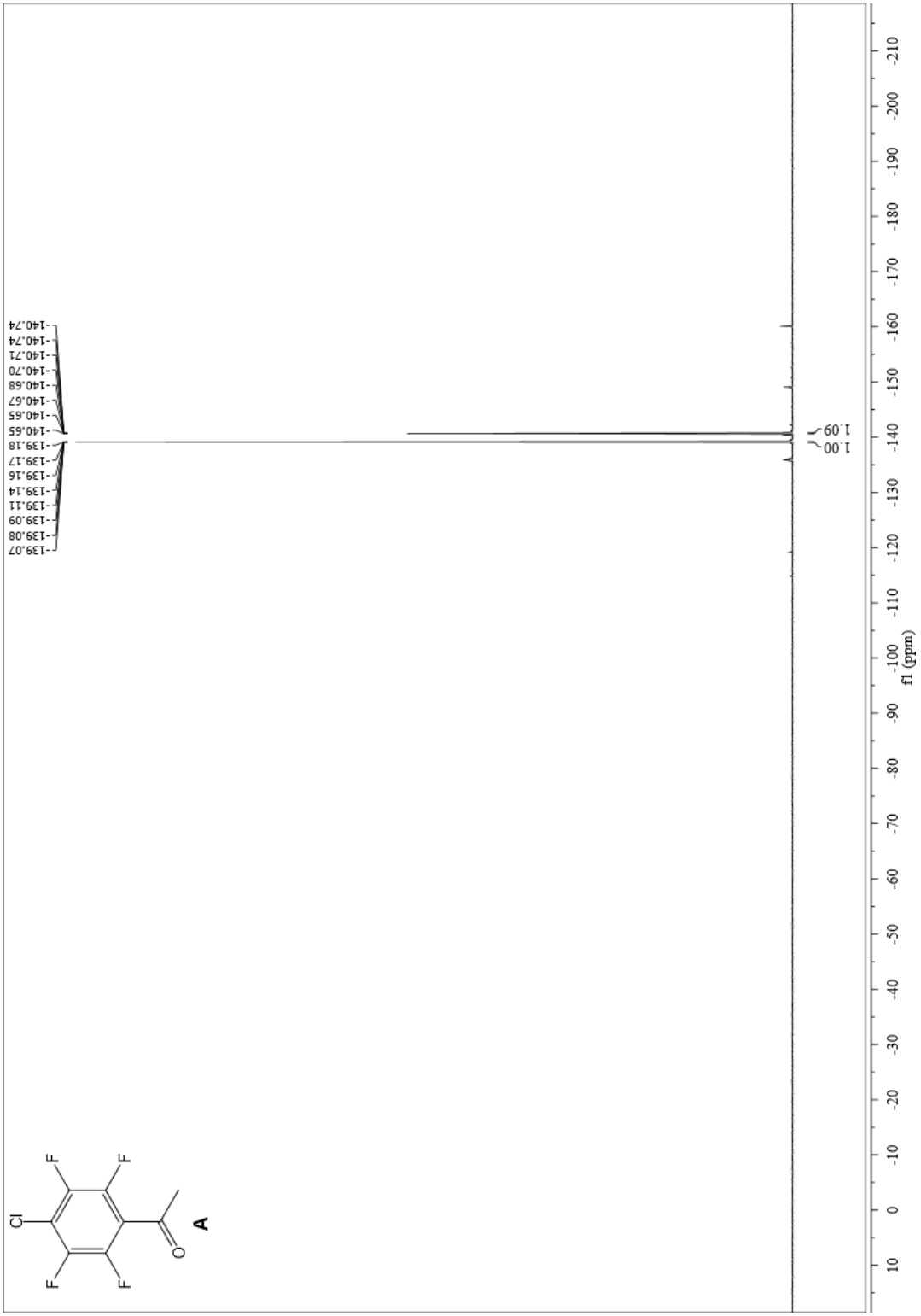




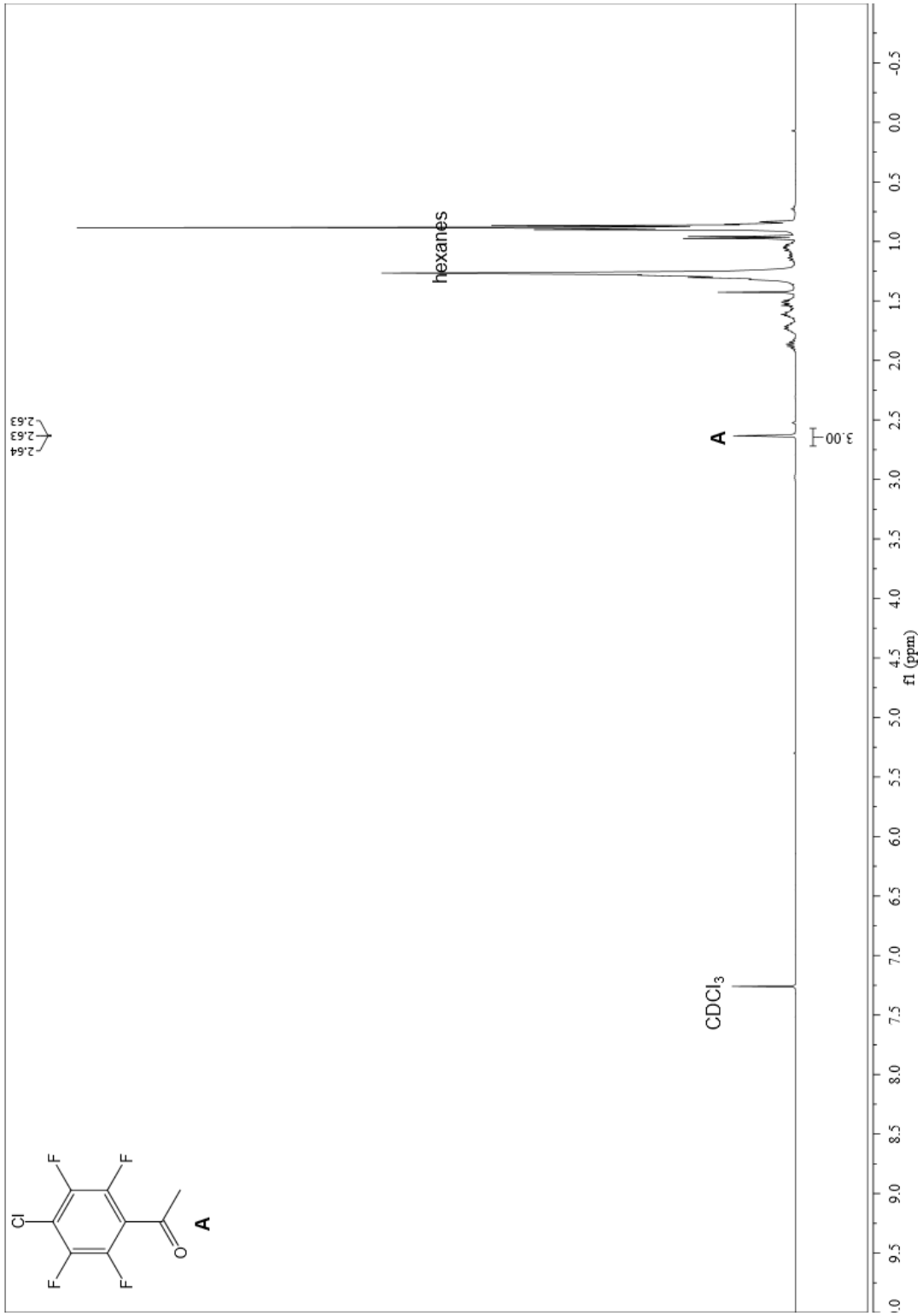
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of crude 1-(4-chloro-2,3,5,6-tetrafluorophenyl)ethan-1-one (5.9d) for NMR yield calculation



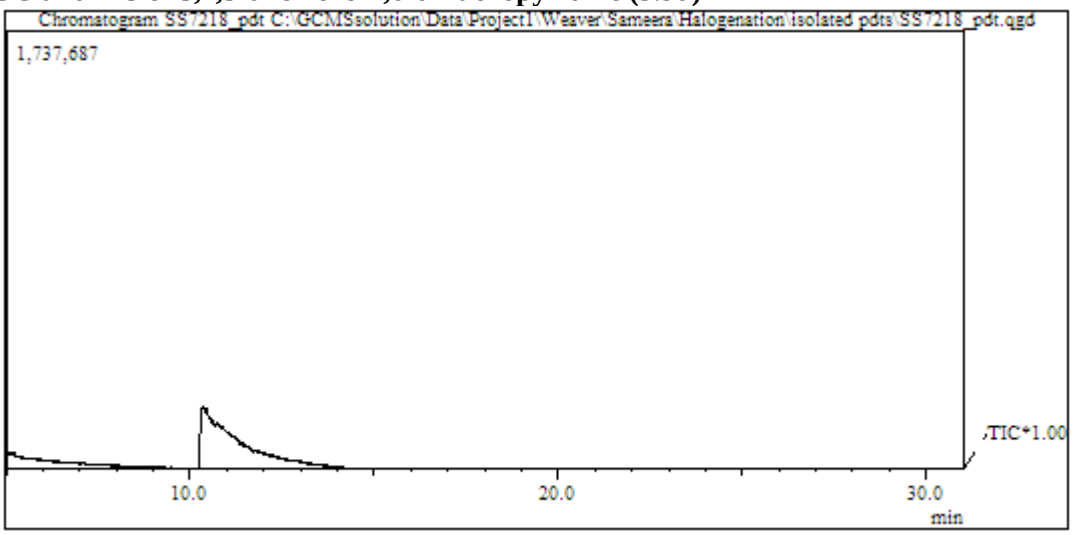
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 1-(4-chloro-2,3,5,6-tetrafluorophenyl)ethan-1-one (5.9d)

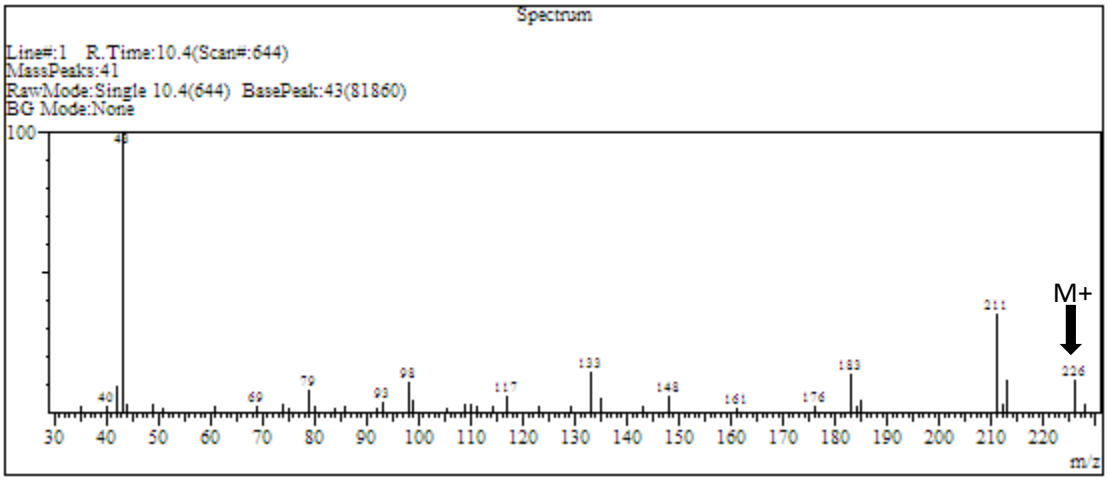


^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 1-(4-chloro-2,3,5,6-tetrafluorophenyl)ethan-1-one (5.9d)

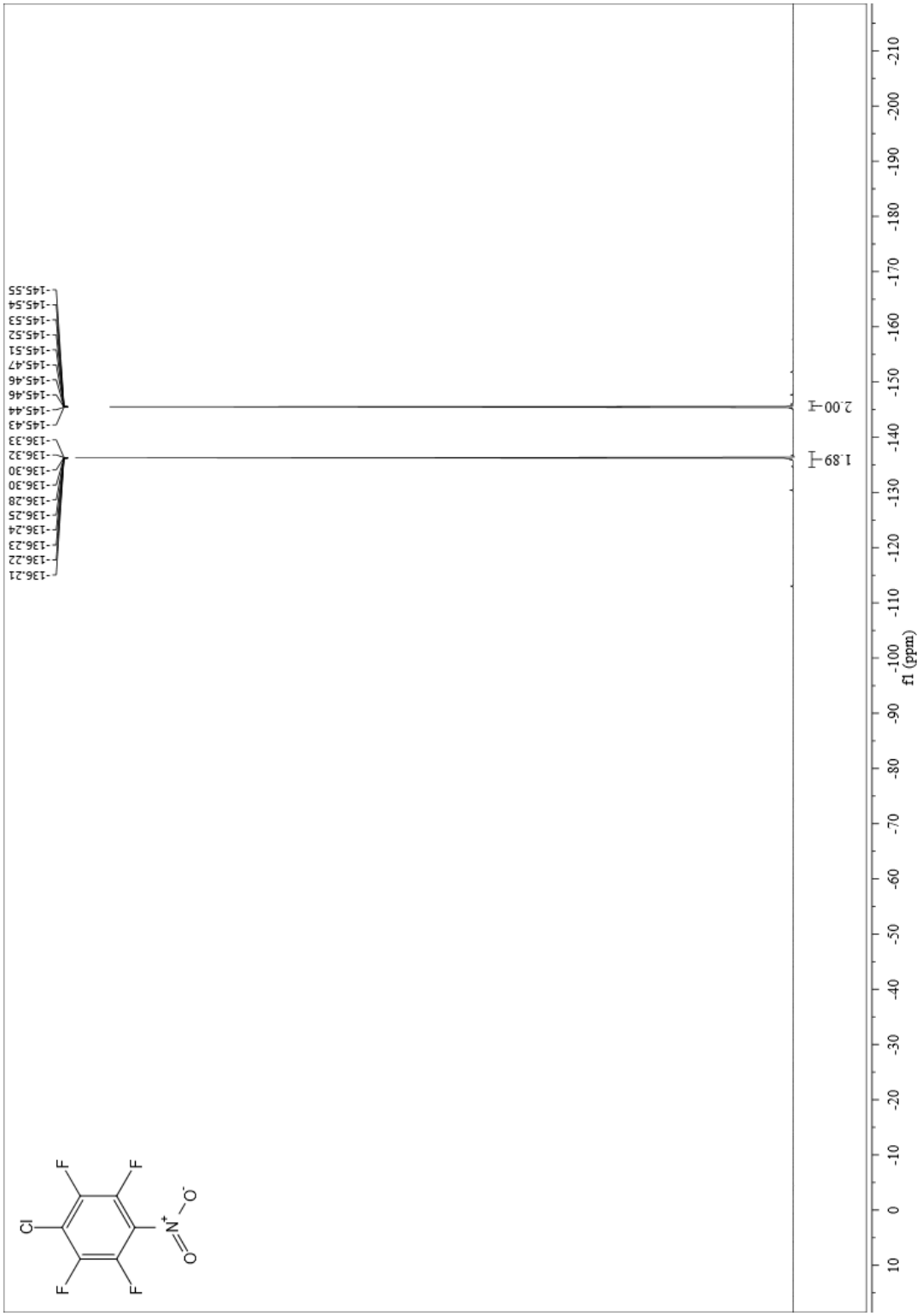


GC and MS of 3,4,5-trichloro-2,6-difluoropyridine (5.9d)

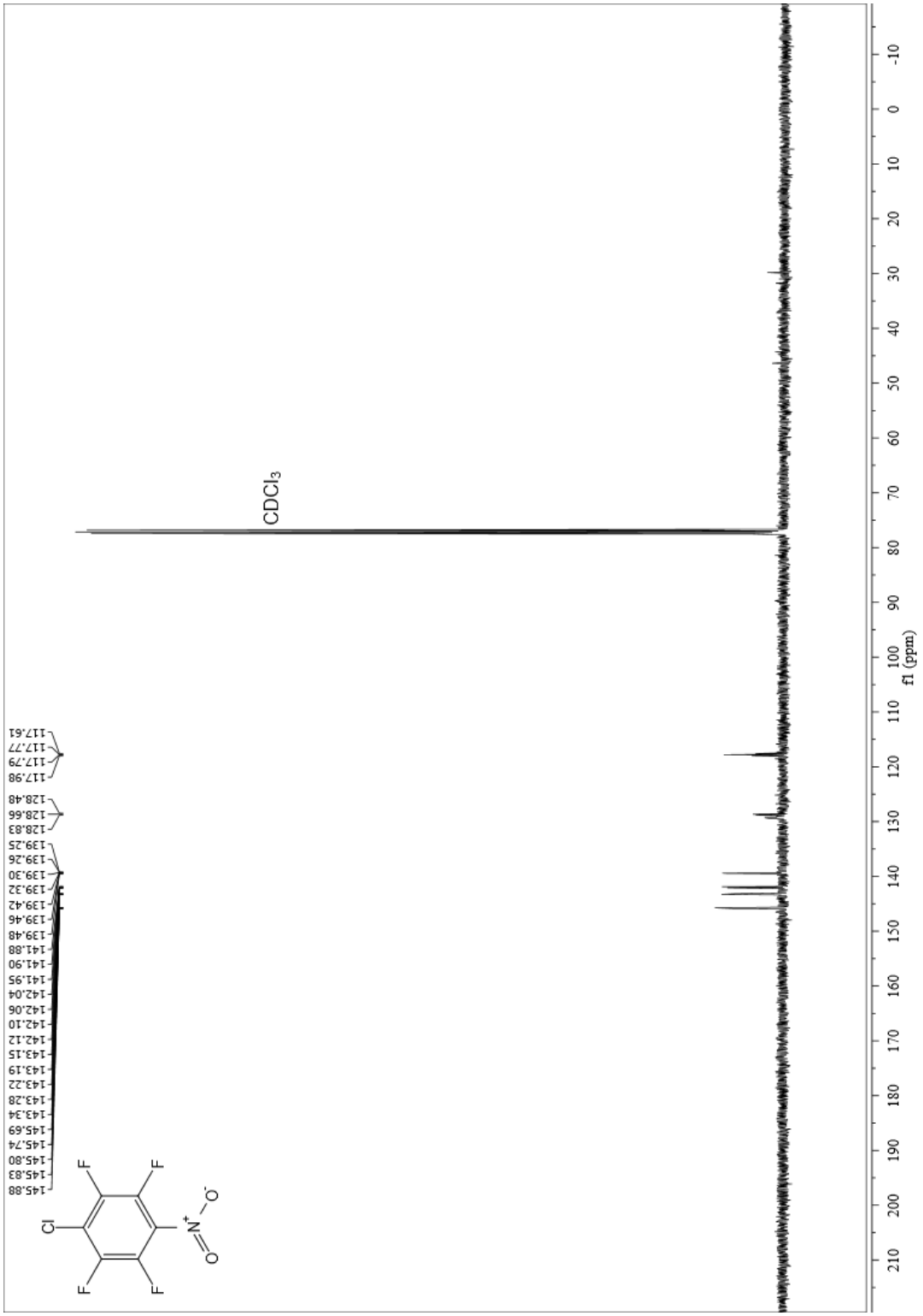




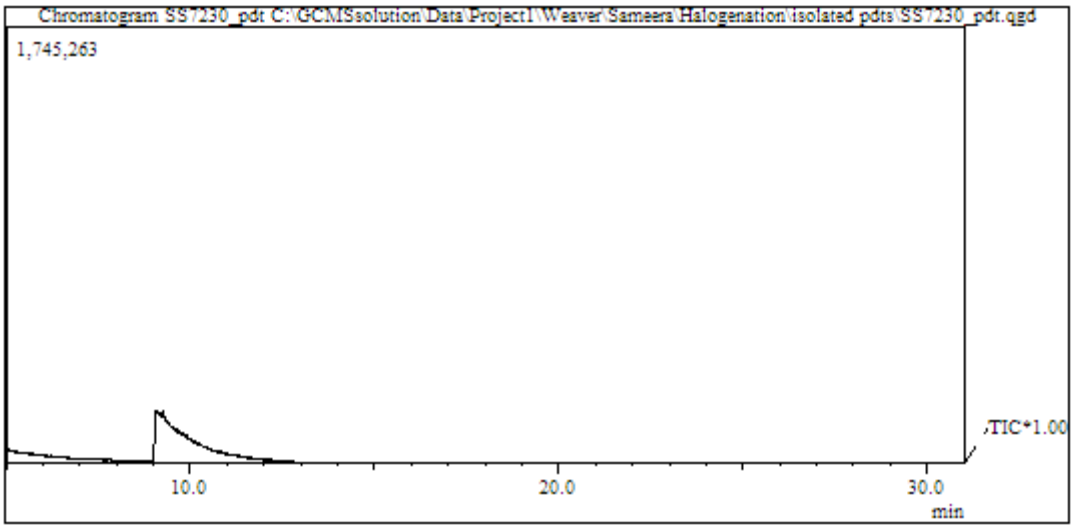
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 1-chloro-2,3,5,6-tetrafluoro-4-nitrobenzene (5.9e)

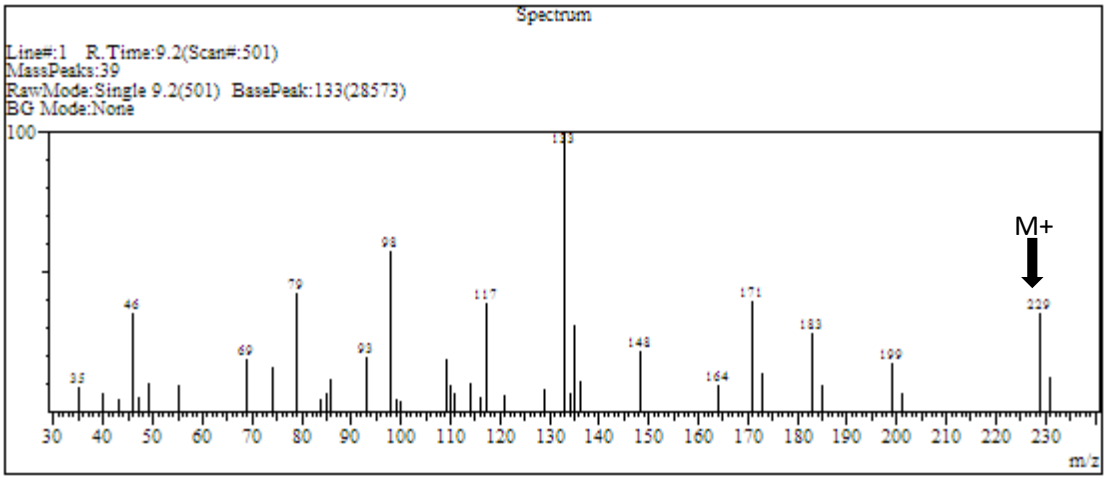


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 1-chloro-2,3,5,6-tetrafluoro-4-nitrobenzene (5.9e)

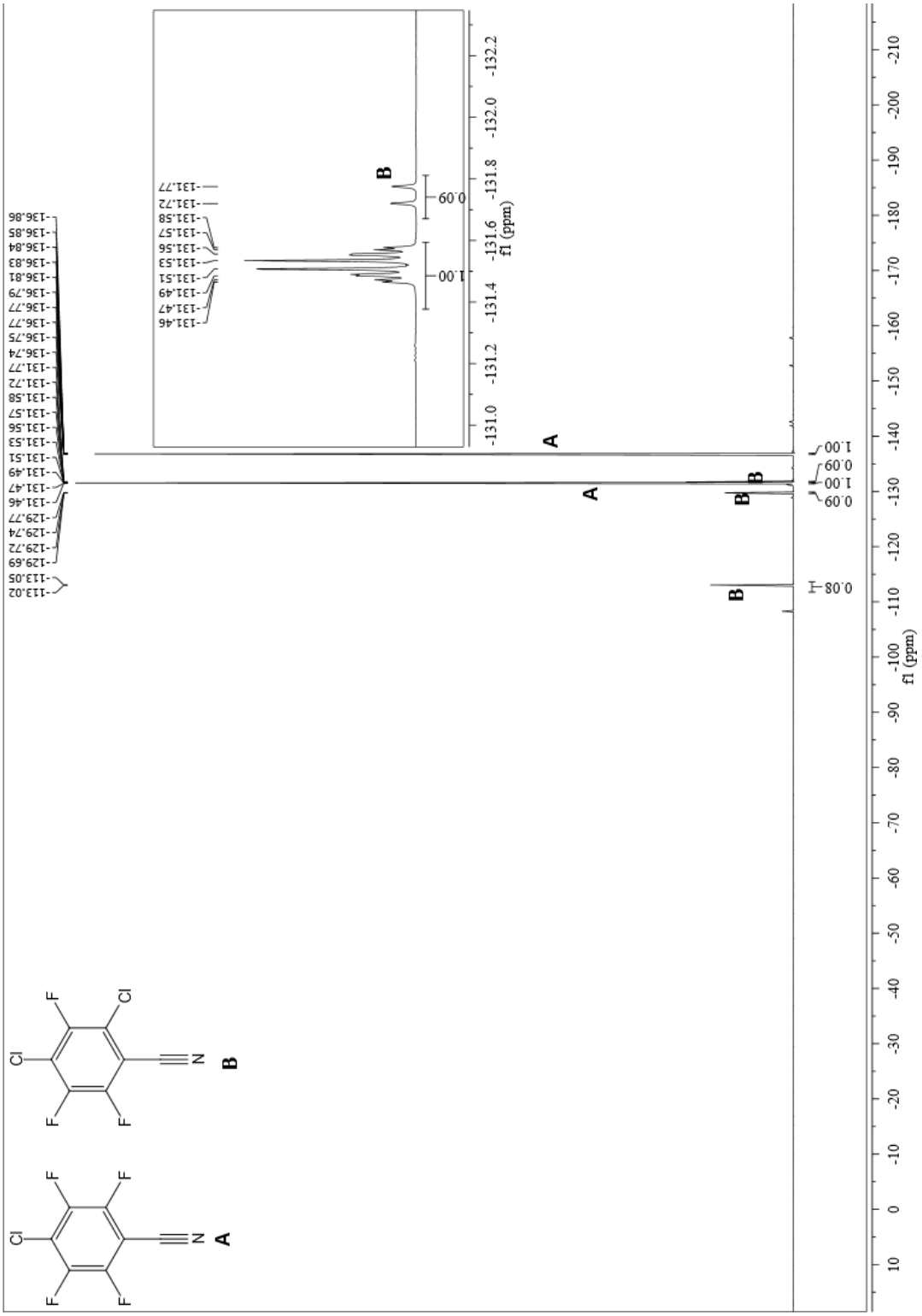


GC and MS of 1-chloro-2,3,5,6-tetrafluoro-4-nitrobenzene (5.9e)

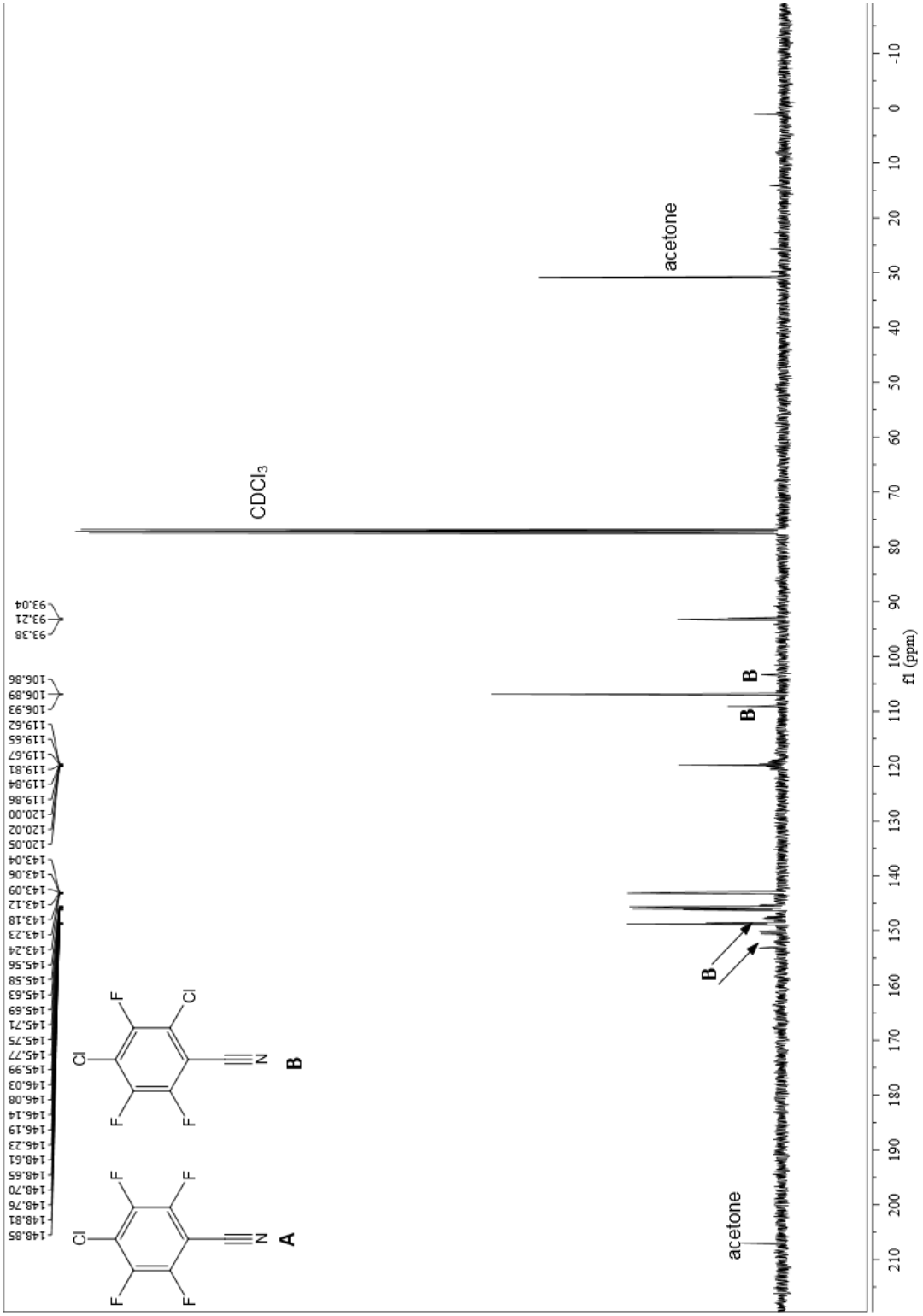




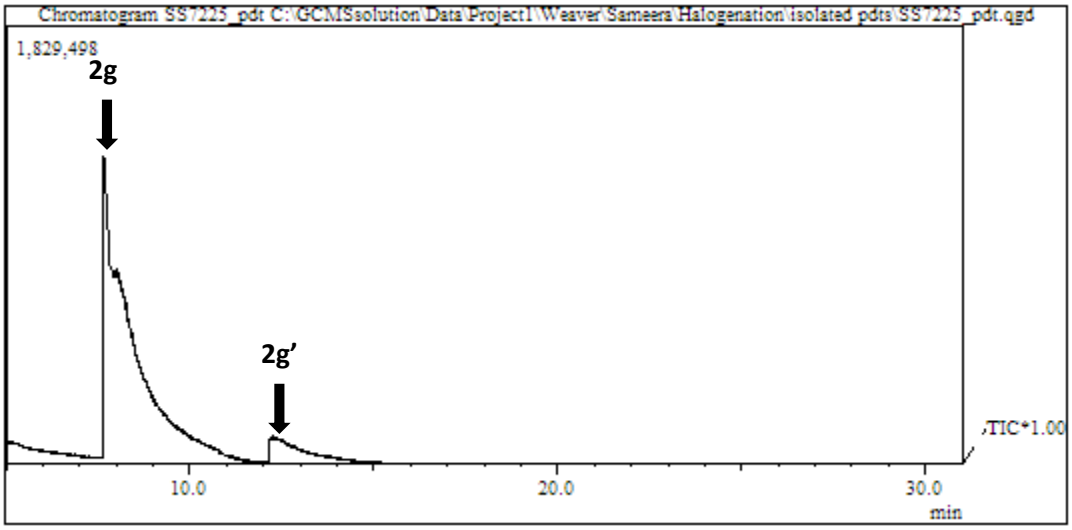
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 4-chloro-2,3,5,6-tetrafluorobenzonitrile (5.9g) and 2,4-dichloro-3,5,6-trifluorobenzonitrile (5.9g')



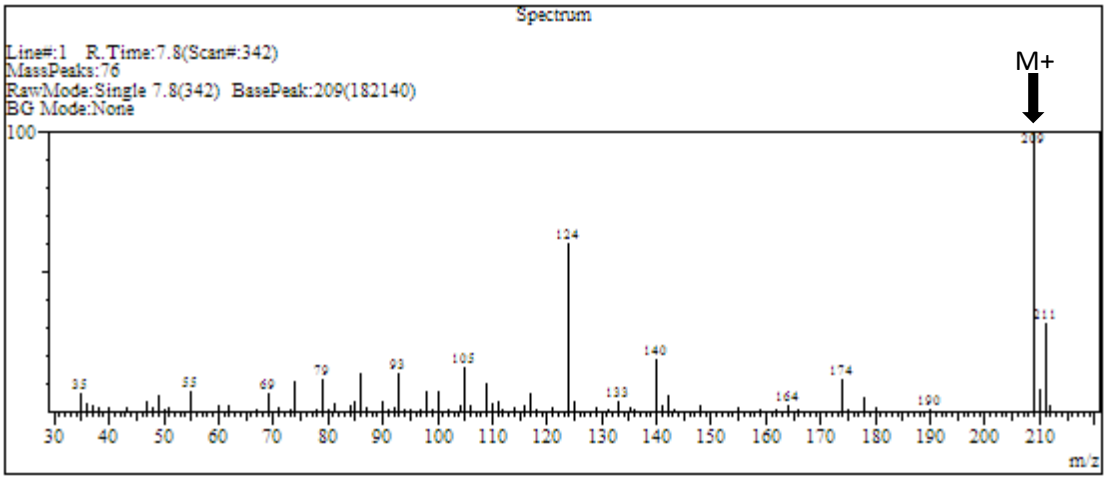
^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 4-chloro-2,3,5,6-tetrafluorobenzonitrile (5.9g) and 2,4-dichloro-3,5,6-trifluorobenzonitrile (5.9g')



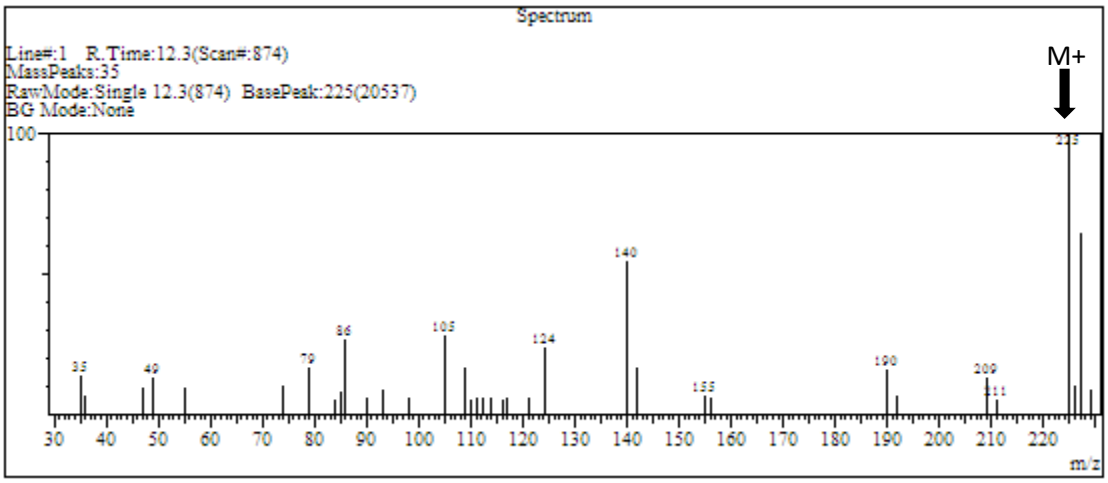
GC of 4-chloro-2,3,5,6-tetrafluorobenzonitrile (5.9g) and 2,4-dichloro-3,5,6-trifluorobenzonitrile (5.9g')



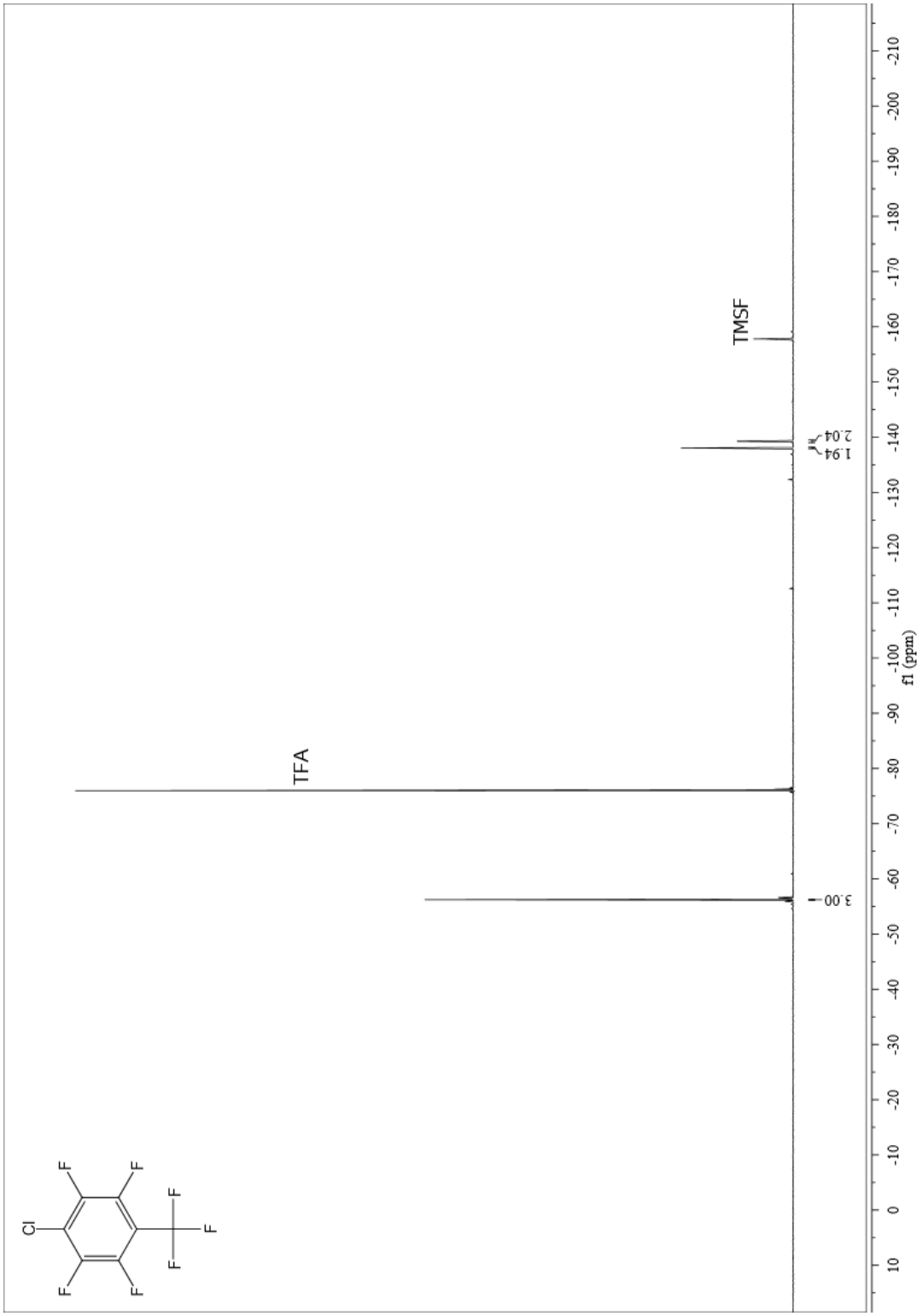
MS of 4-chloro-2,3,5,6-tetrafluorobenzonitrile (5.9g)



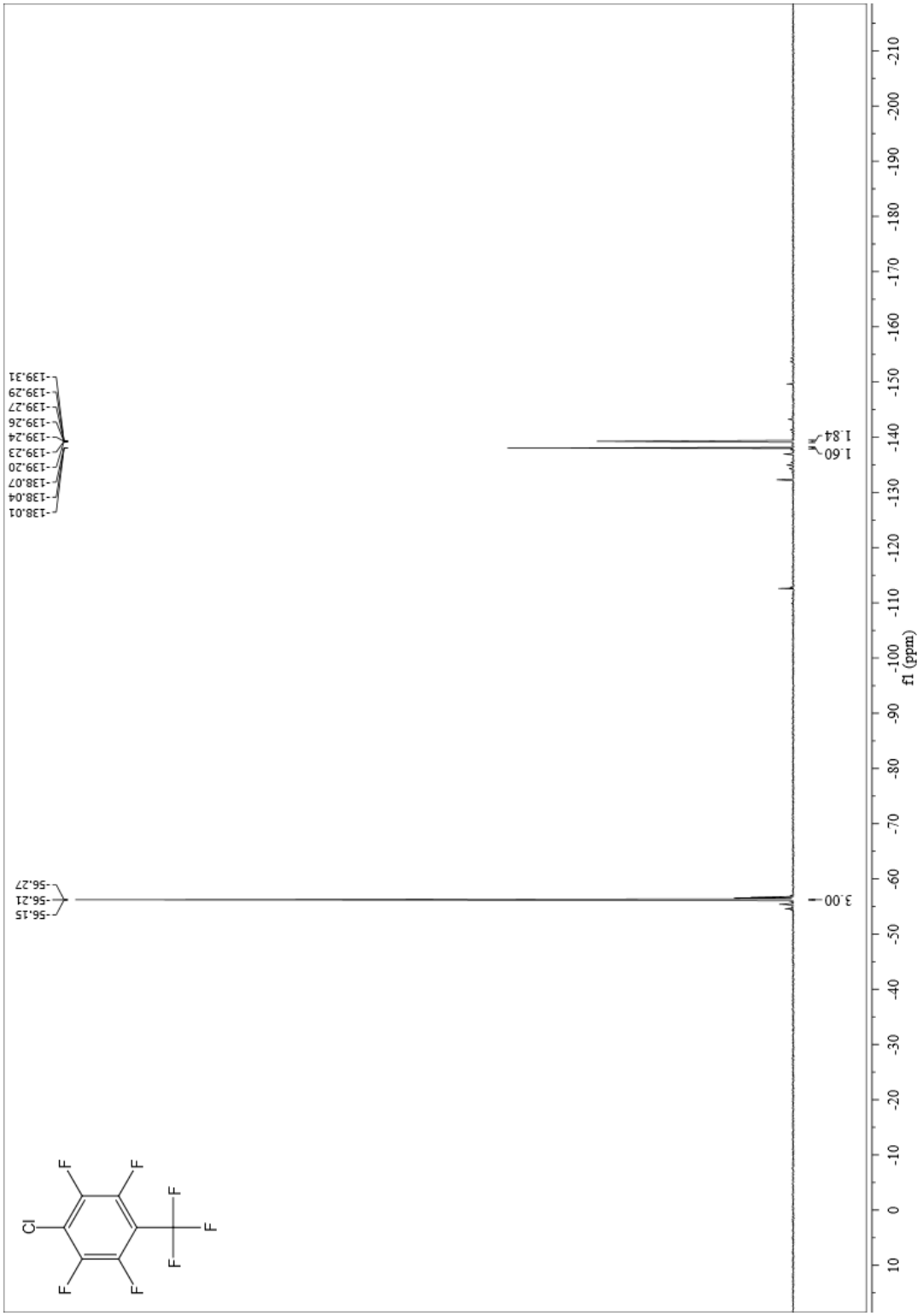
MS of 2,4-dichloro-3,5,6-trifluorobenzonitrile (5.9g')



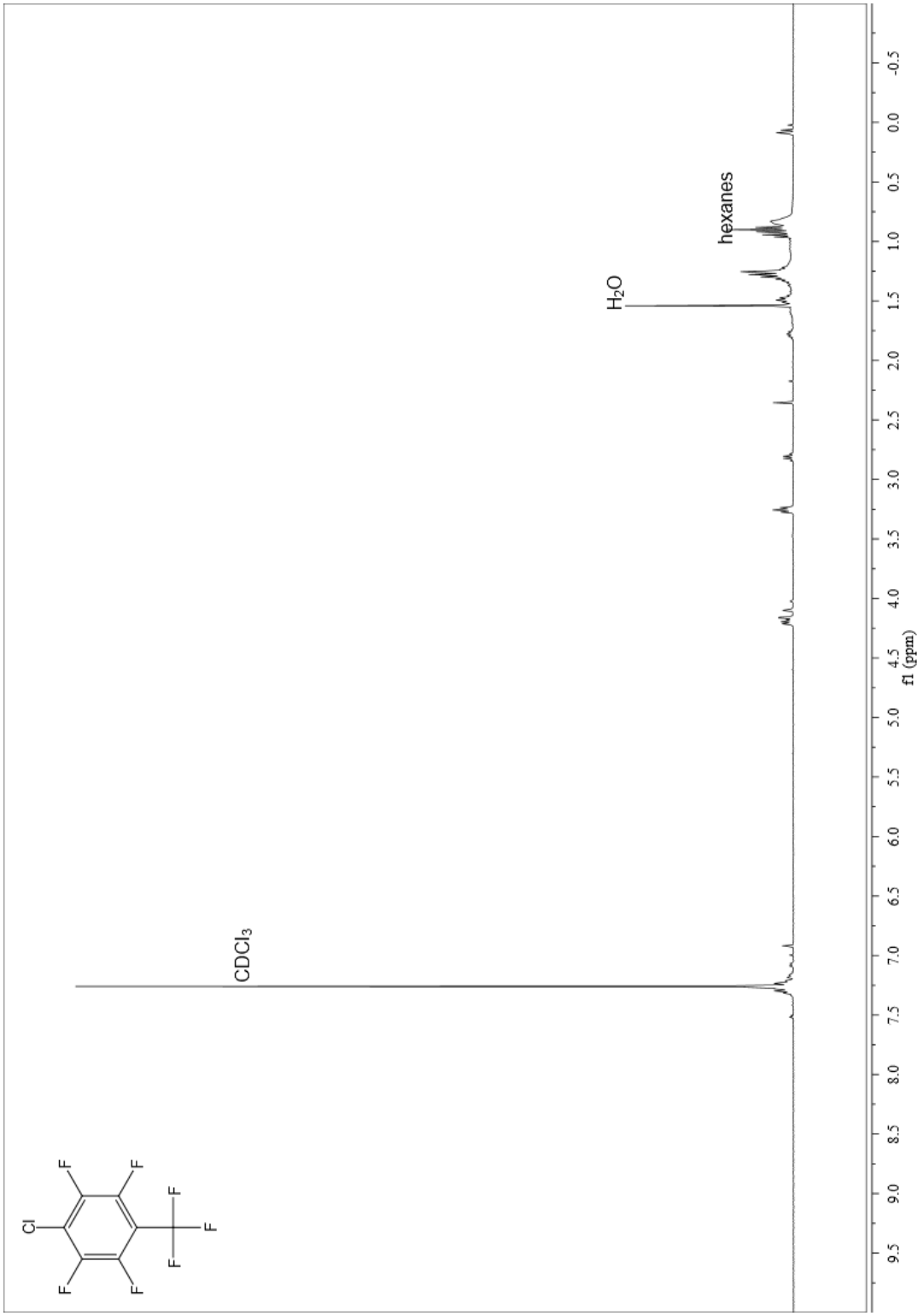
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of crude 1-chloro-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (5.9f) for NMR yield calculation



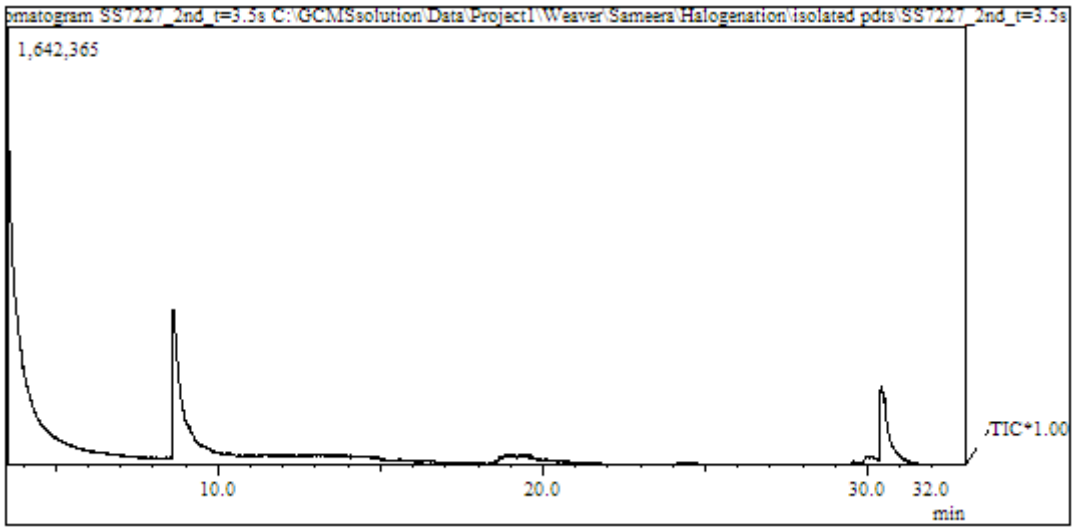
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 1-chloro-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (5.9f)

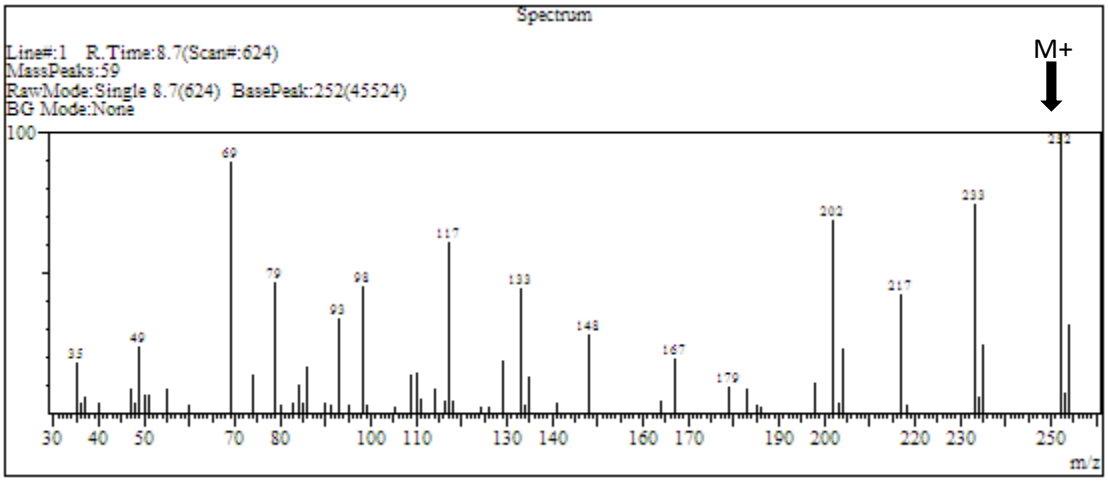


^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 1-chloro-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (5.9f)

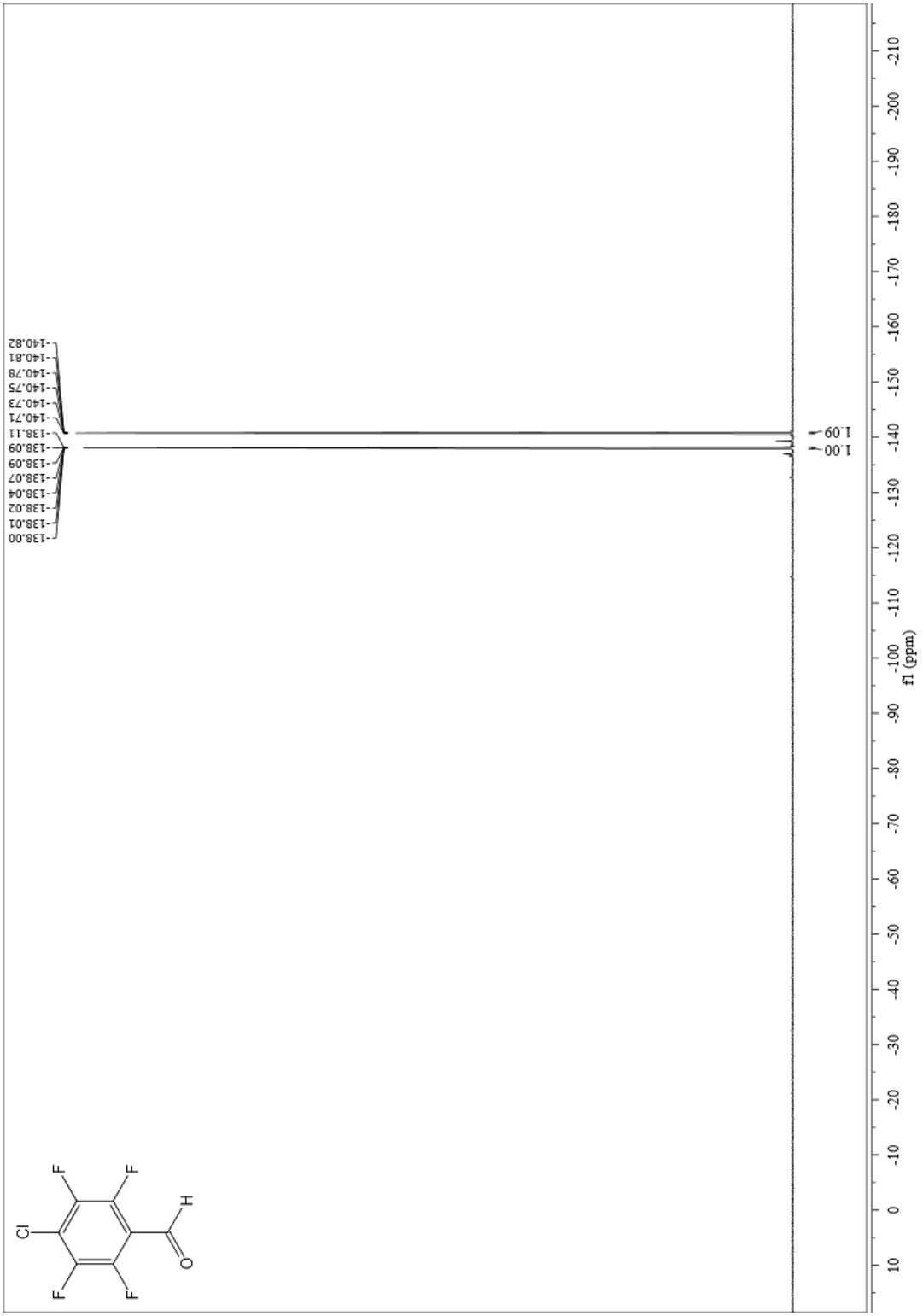


GC and MS of GC and MS of 1-chloro-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (5.9f)

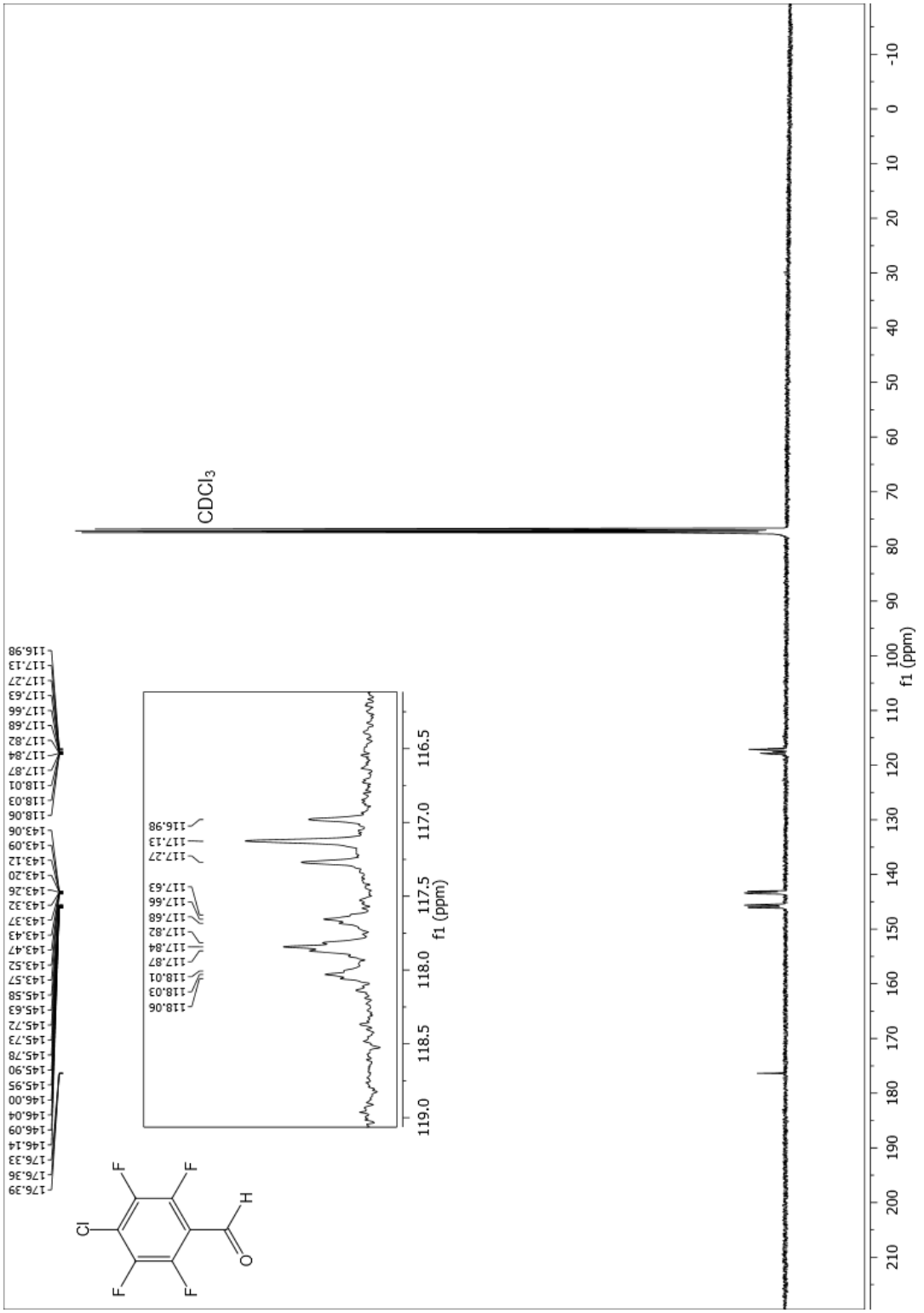




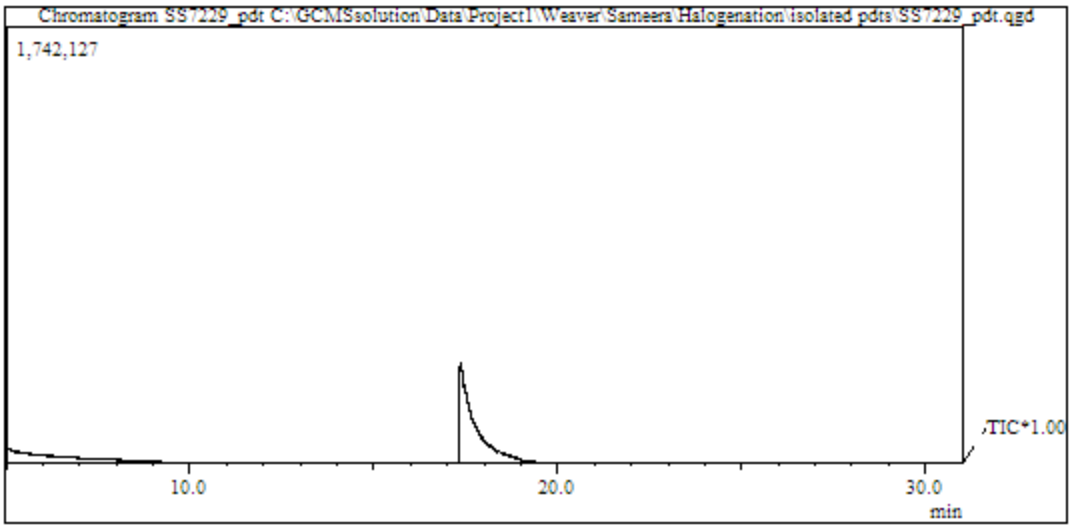
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 4-chloro-2,3,5,6-tetrafluorobenzaldehyde (5.9h)

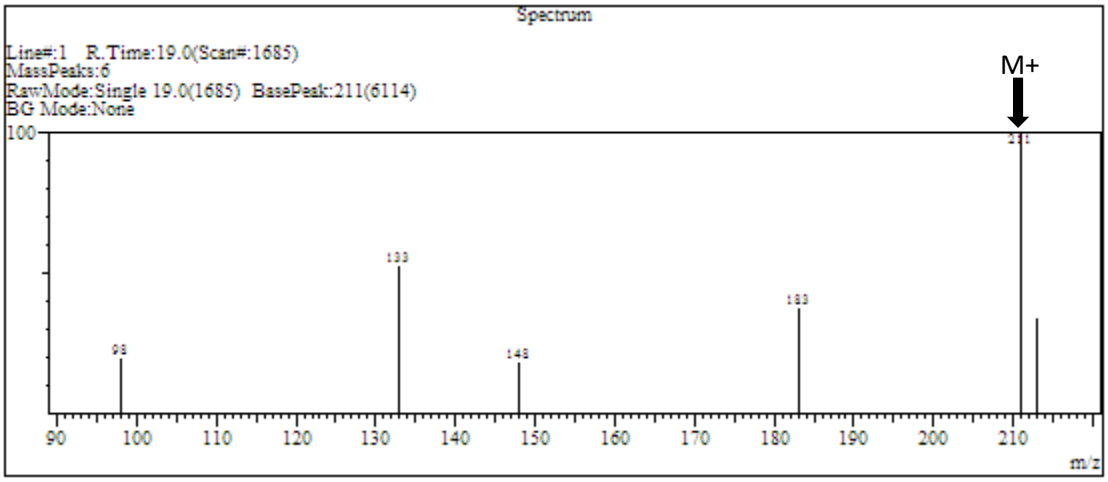


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 4-chloro-2,3,5,6-tetrafluorobenzaldehyde (5.9h)

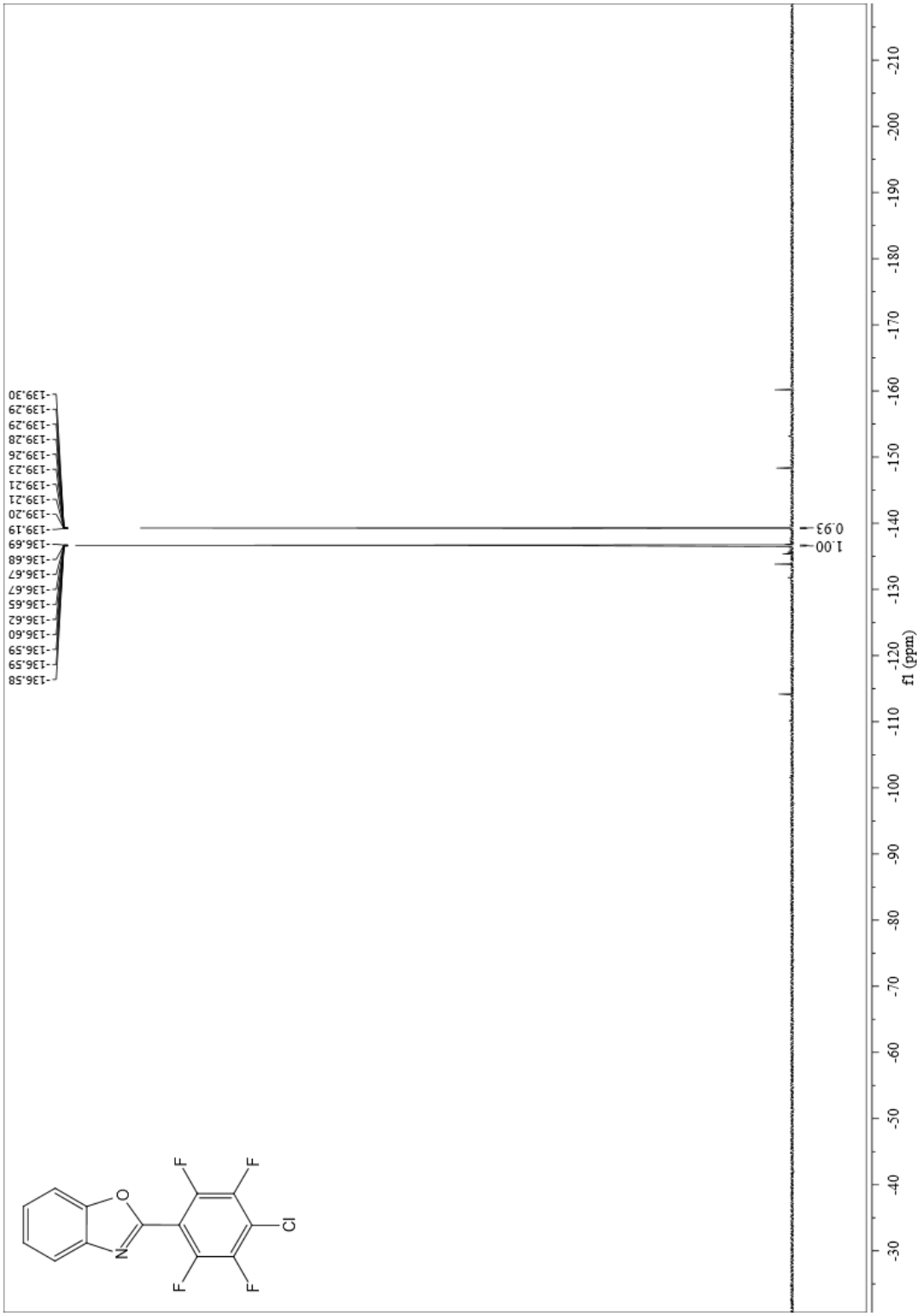


GC and MS of GC and MS of 4-chloro-2,3,5,6-tetrafluorobenzaldehyde (5.9h)

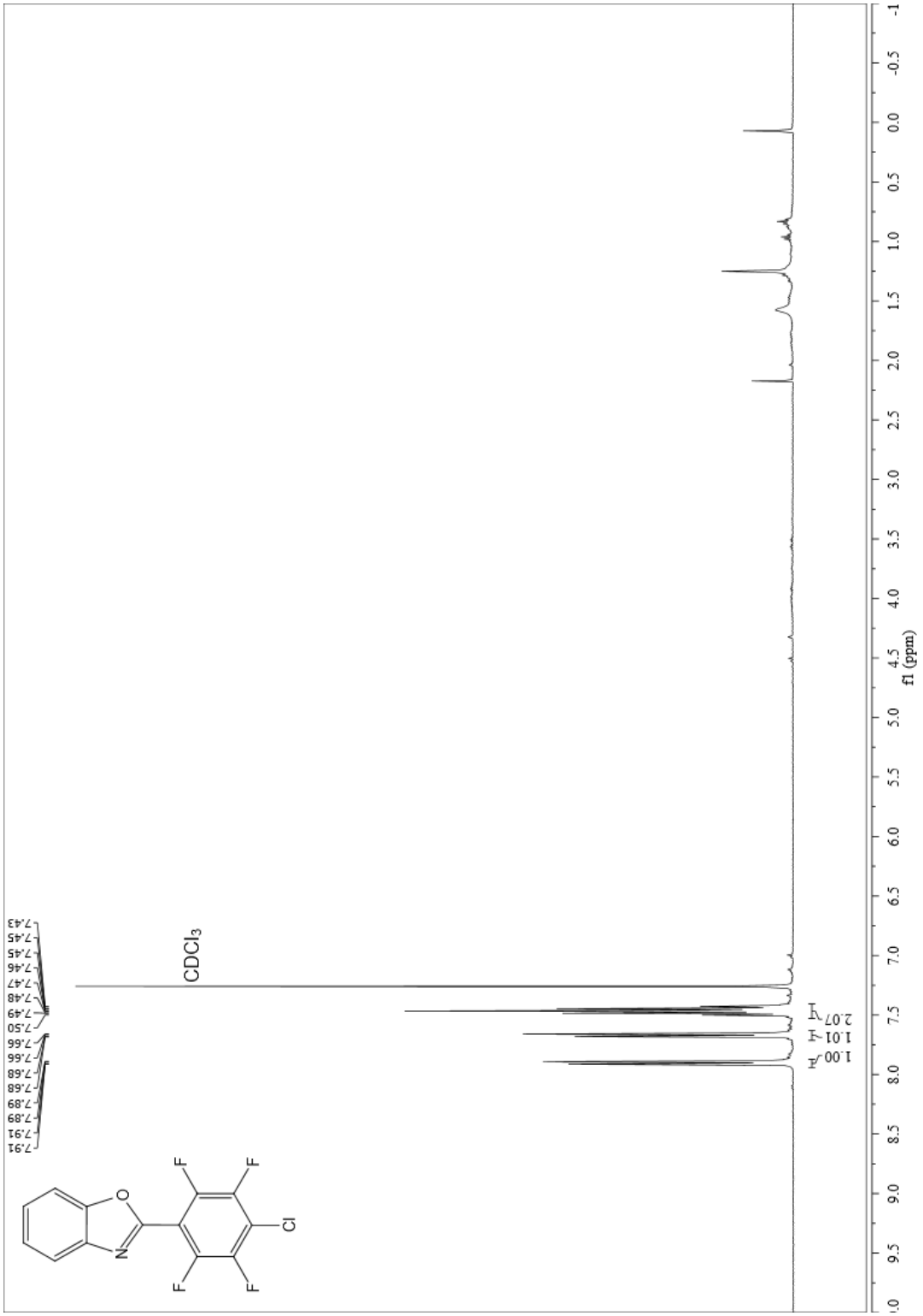




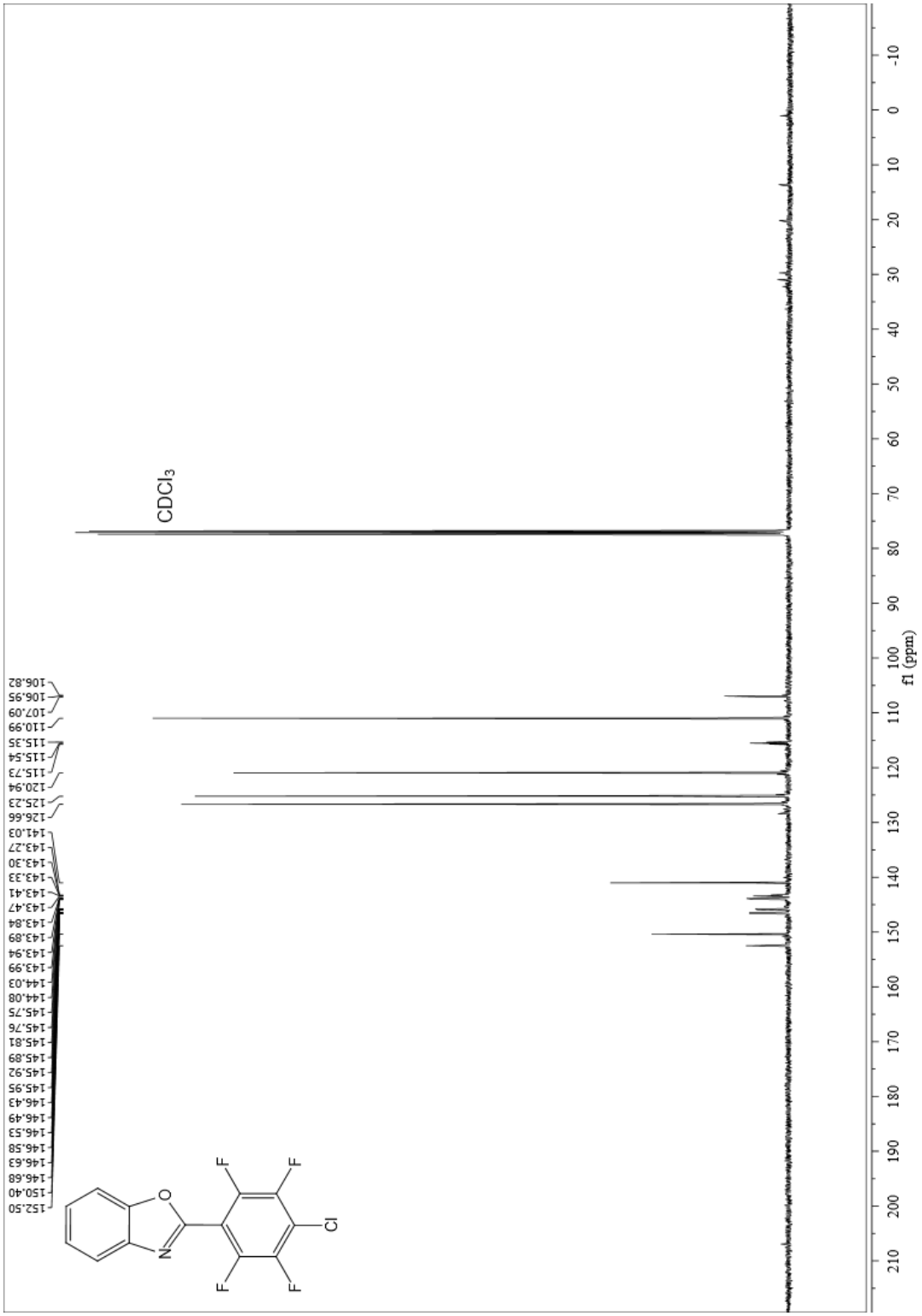
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]oxazole (5.9i)



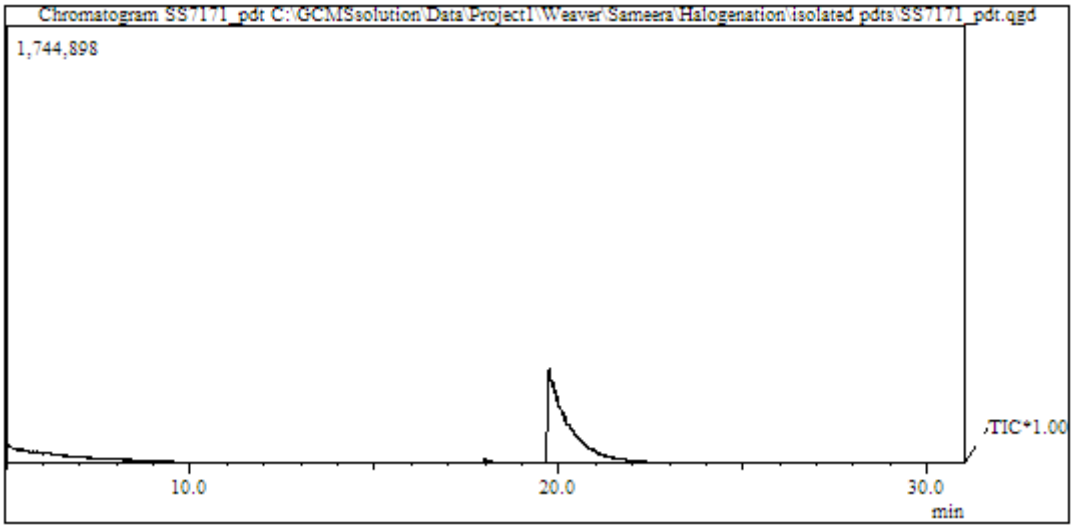
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]oxazole (5.9i)

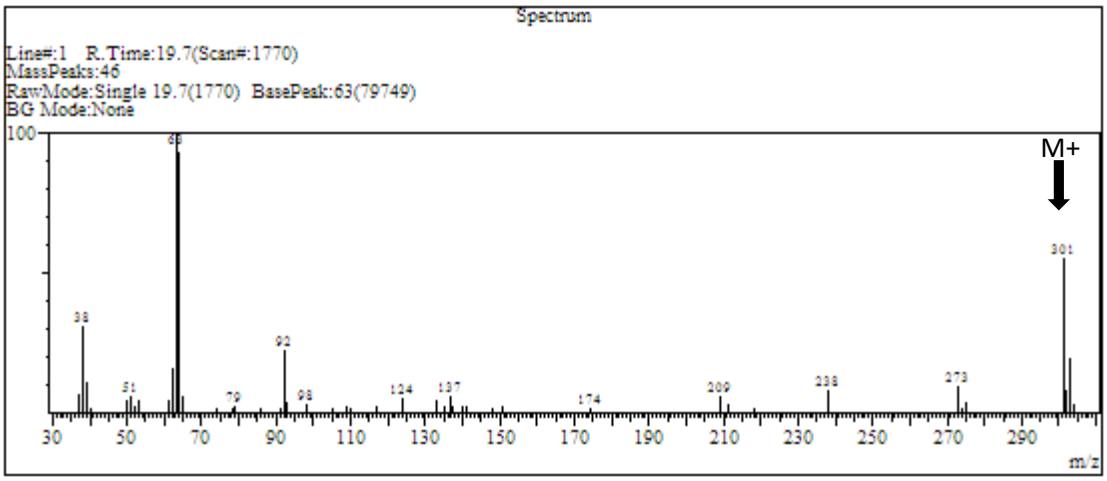


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]oxazole (5.9i)

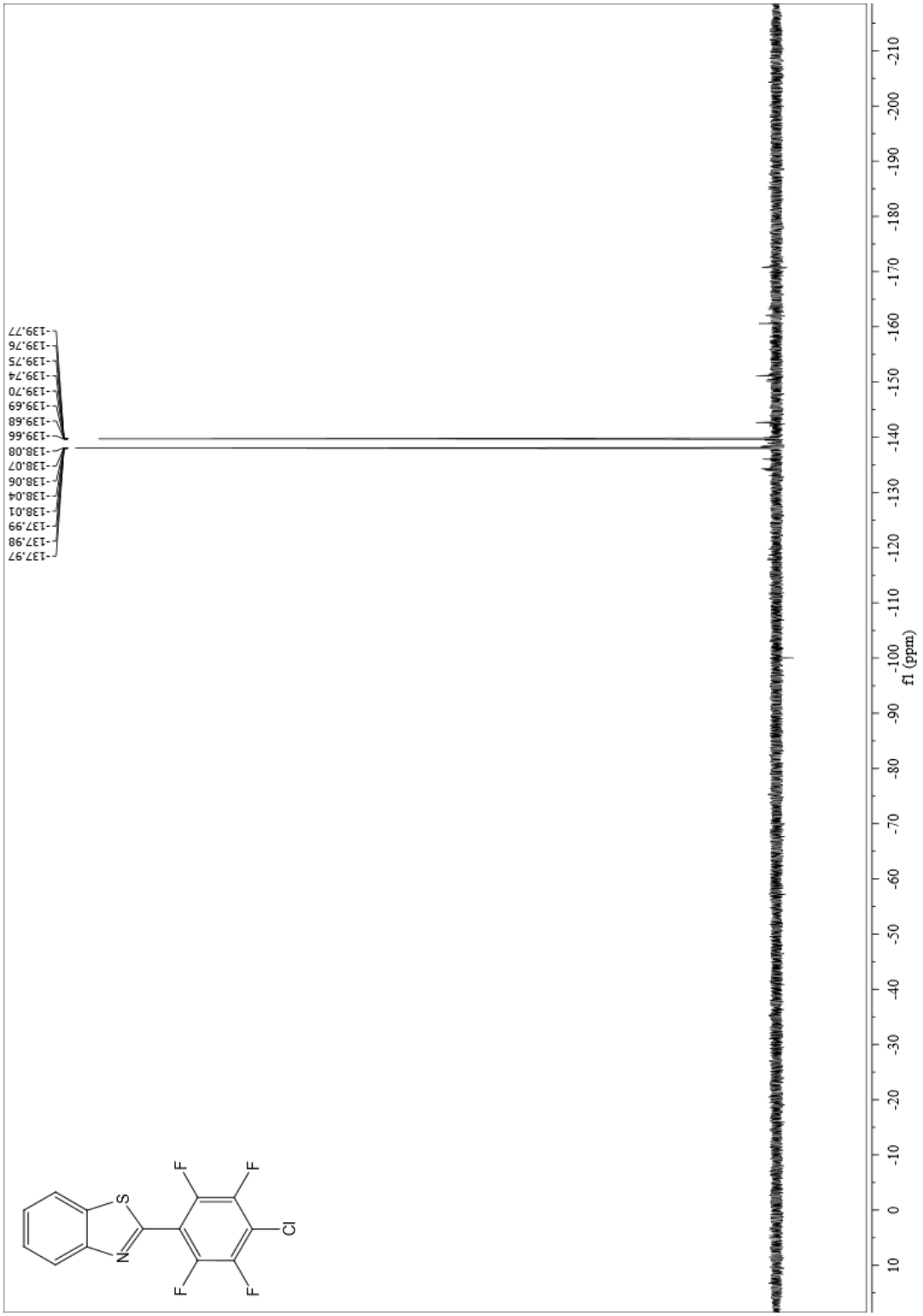


GC and MS of GC and MS of 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]oxazole (5.9i)

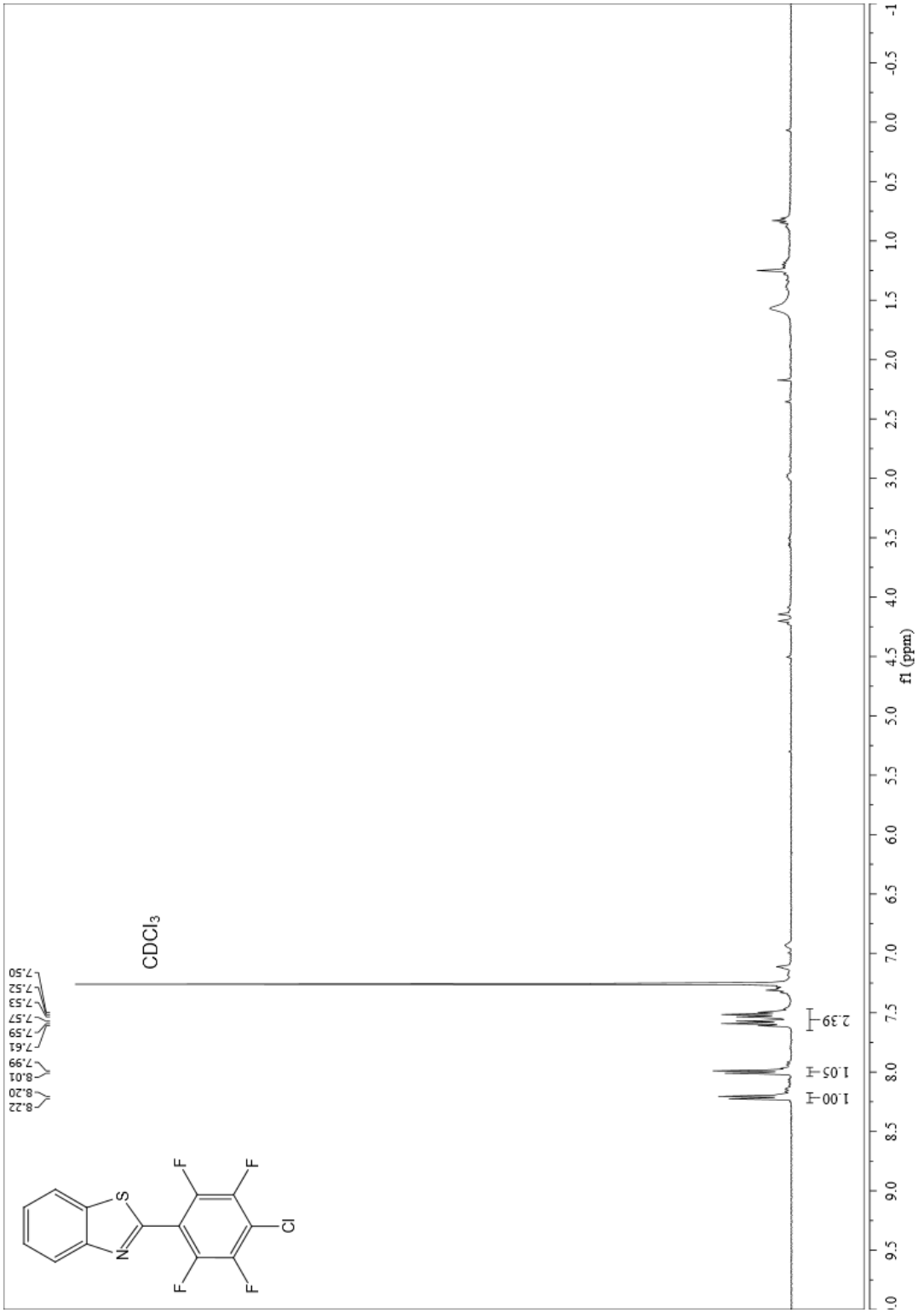




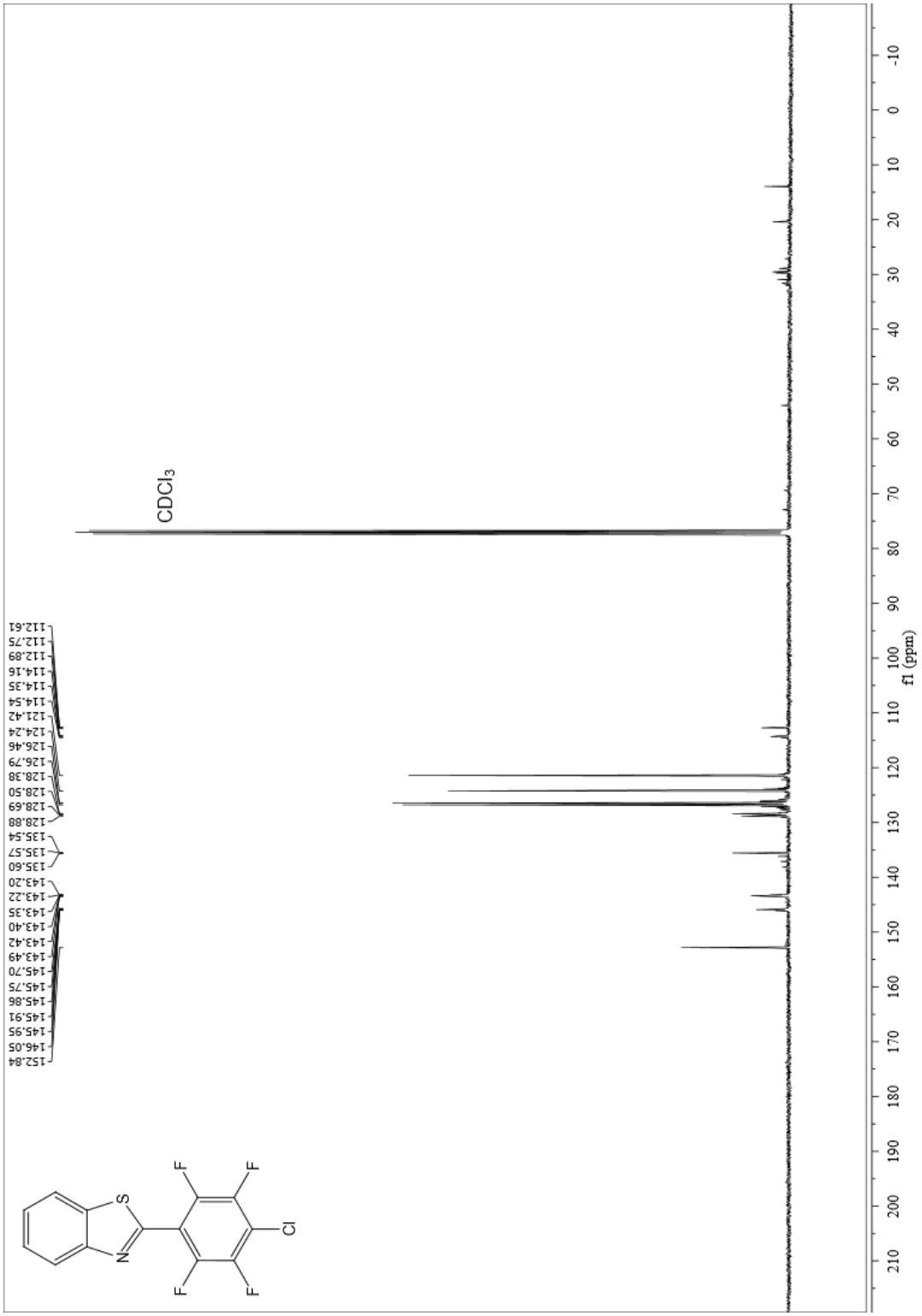
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]thiazole (5.9j)



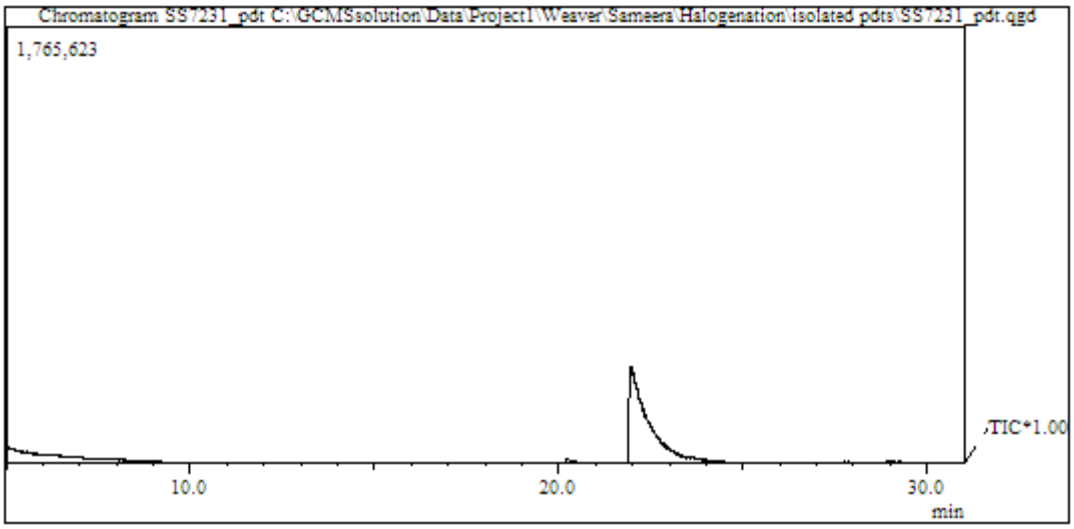
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]thiazole (5.9j)

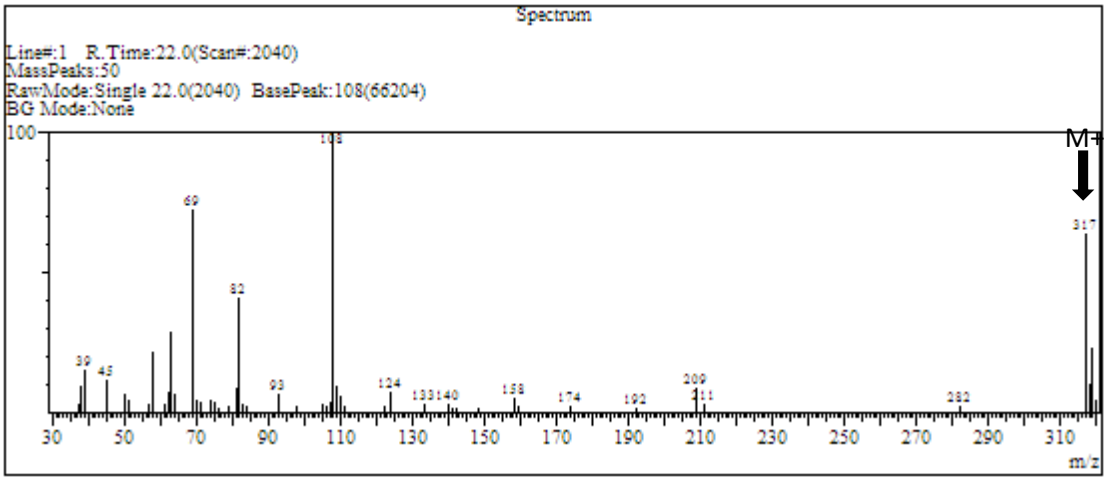


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]thiazole (5.9j)

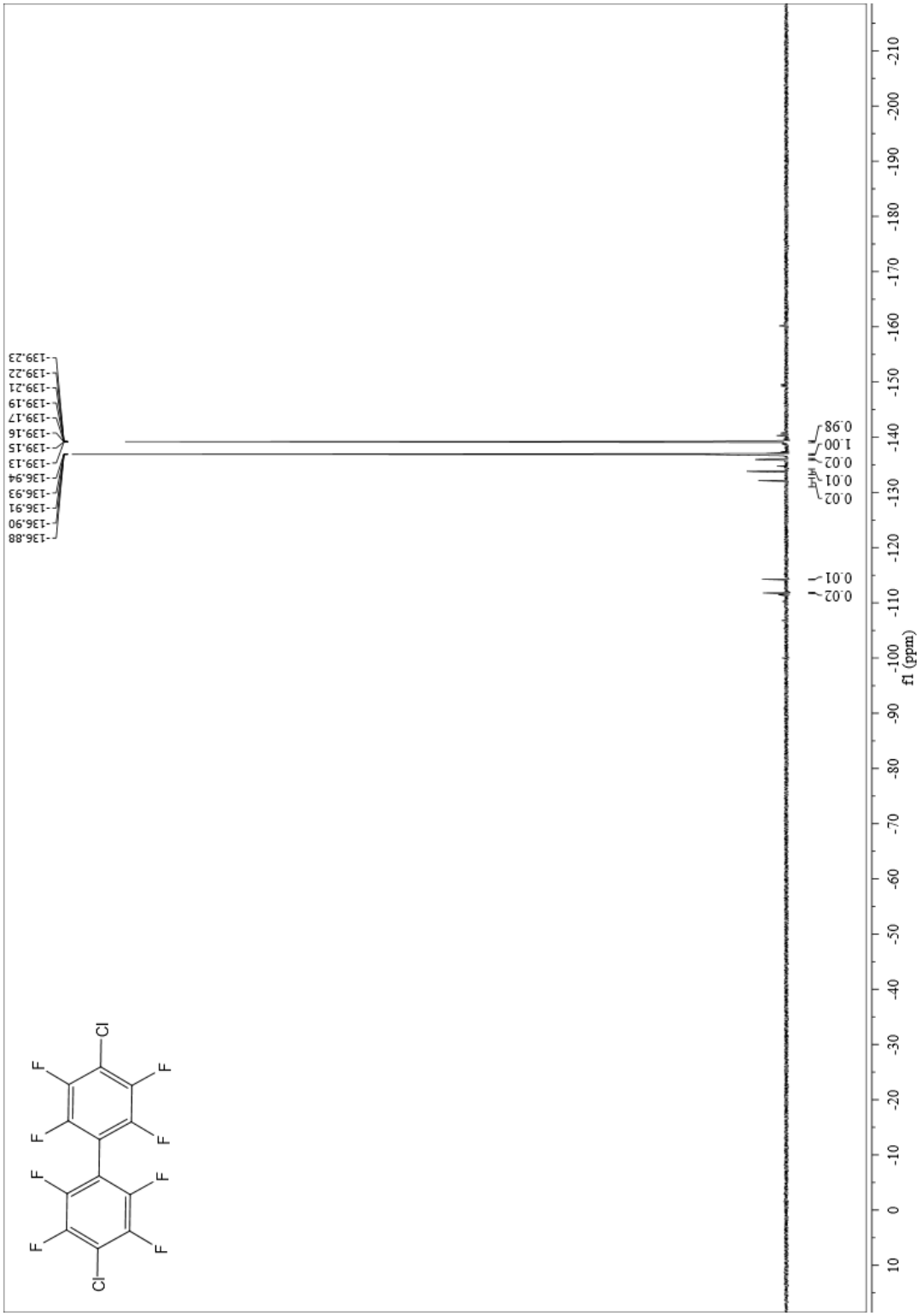


GC and MS of GC and MS of 2-(4-chloro-2,3,5,6-tetrafluorophenyl)benzo[*d*]thiazole (5.9j)

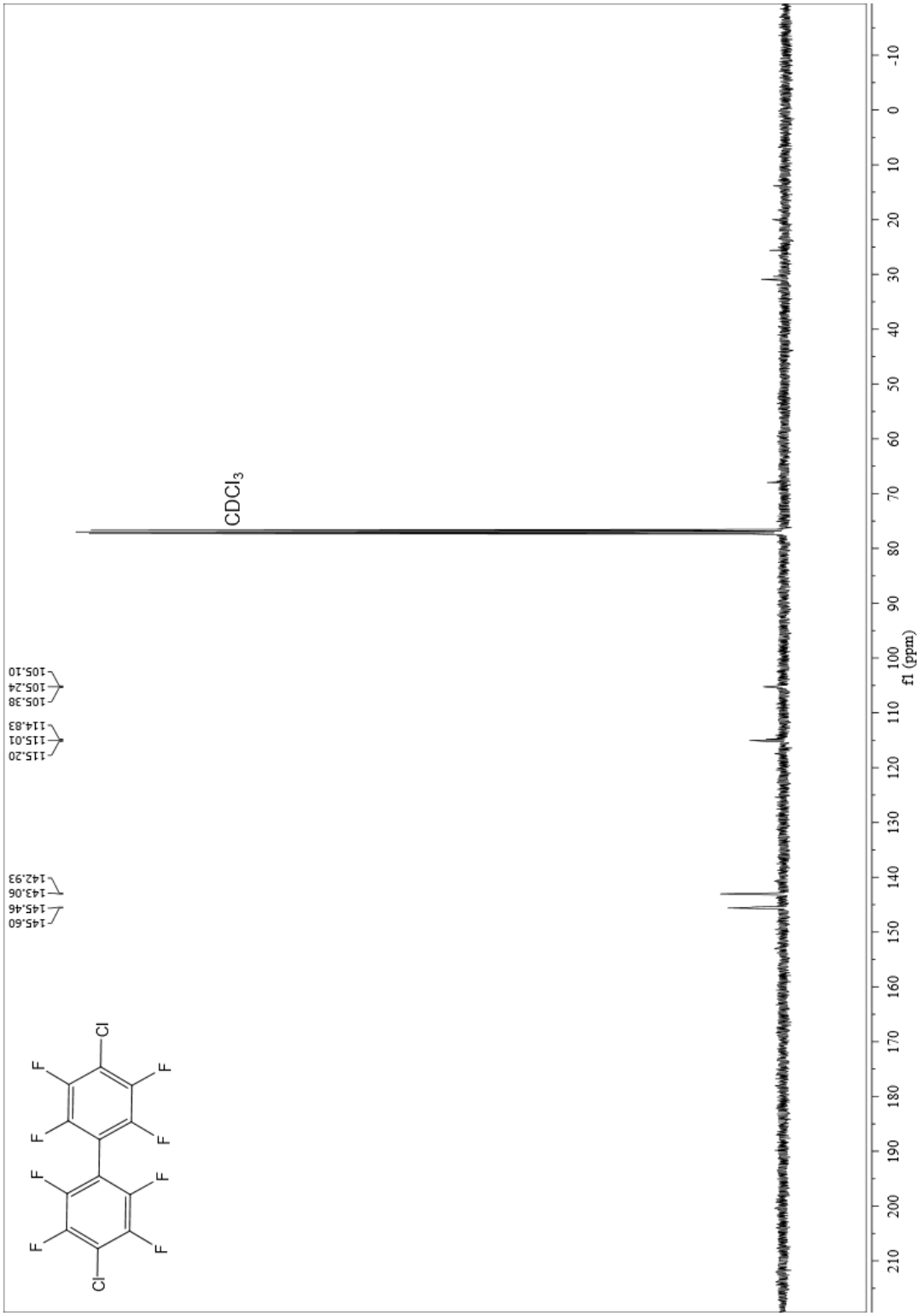




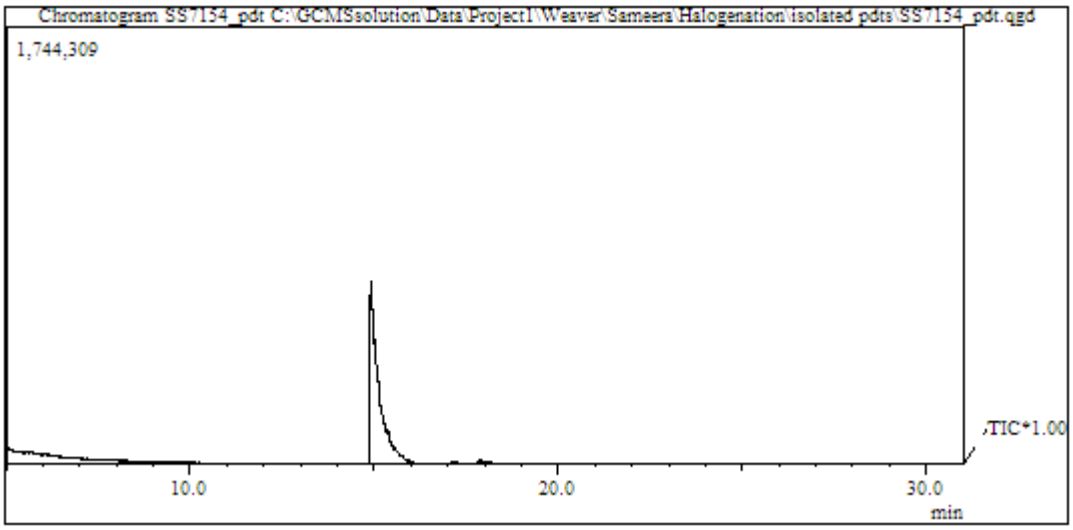
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 4,4'-dichloro-2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl (5.9k)

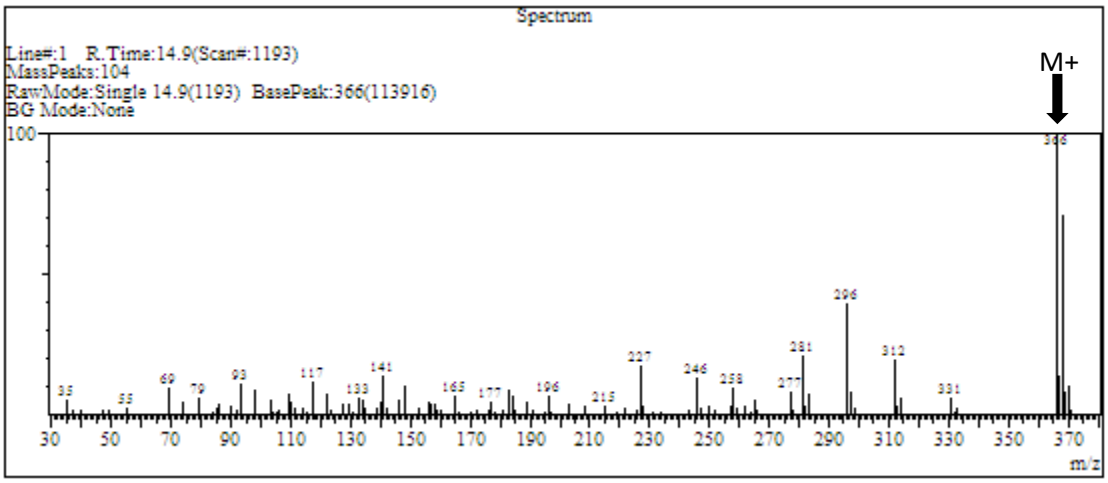


^{1}3C NMR (376 MHz, $CDCl_3$, at rt) spectrum of isolated 4,4'-dichloro-2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl (5.9k)

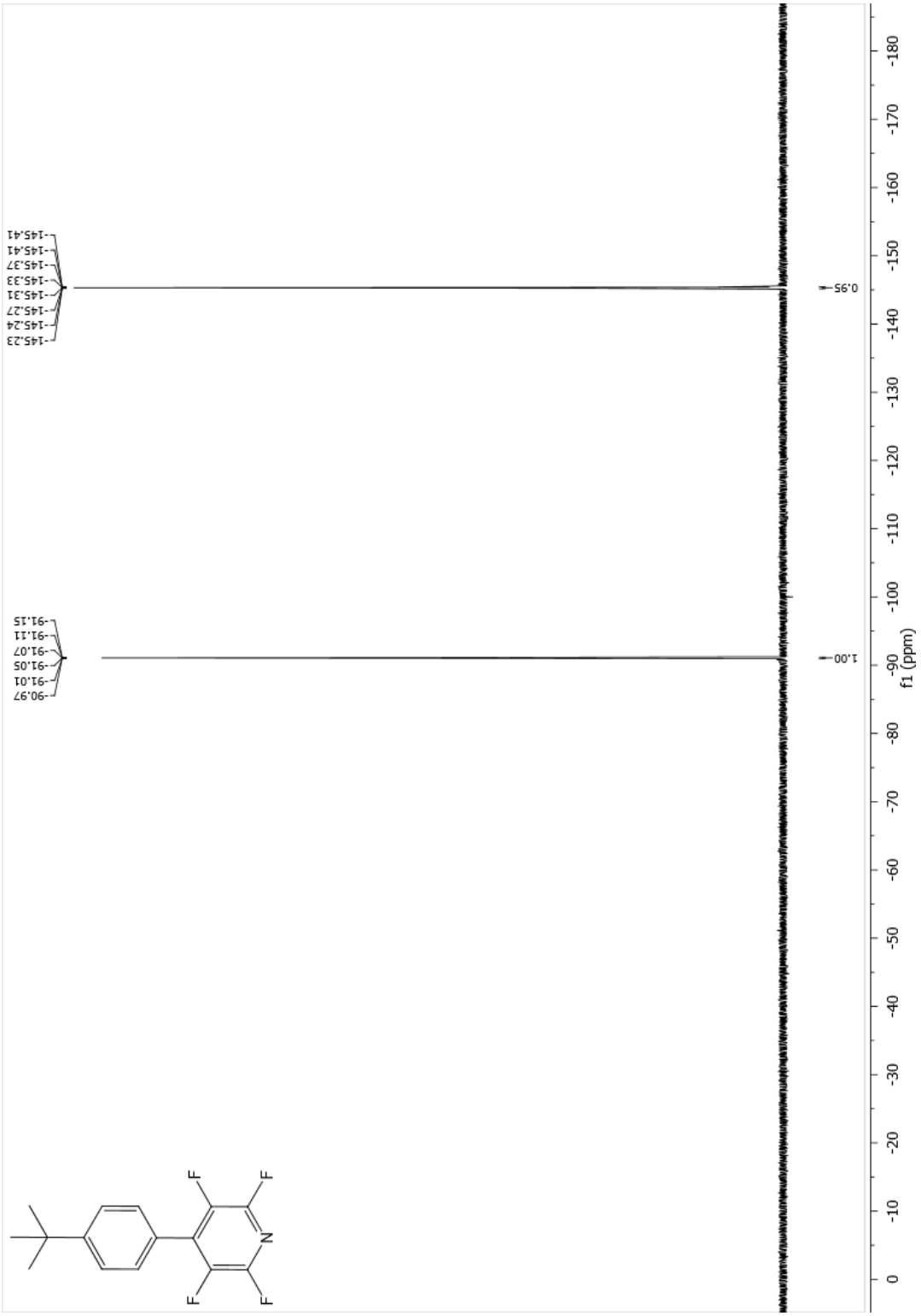


GC and MS of GC and MS of 4,4'-dichloro-2,2',3,3',5,5',6,6'-octafluoro-1,1'-biphenyl (5.9k)

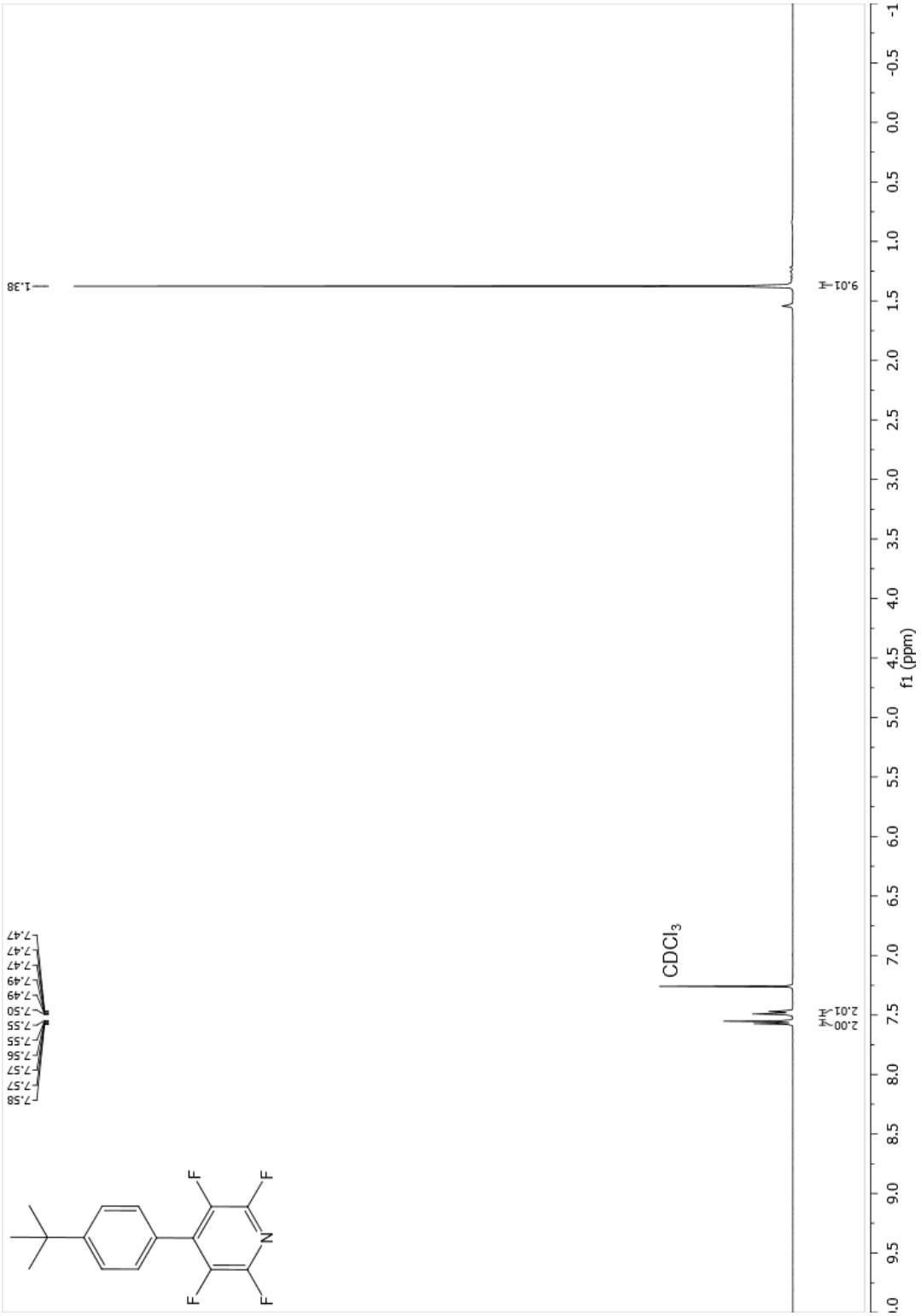




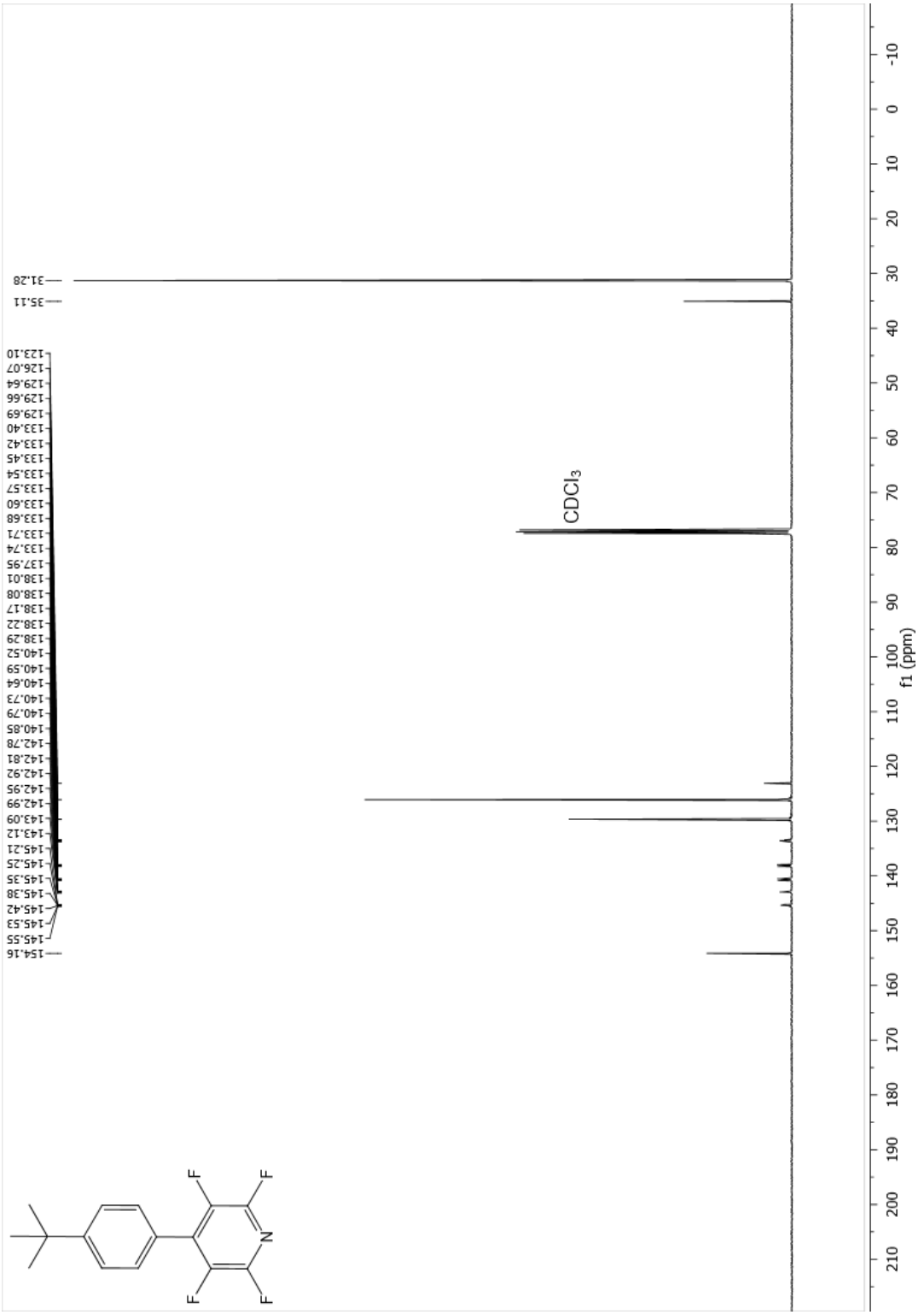
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4-(4-(*tert*-butyl)phenyl)-2,3,5,6-tetrafluoropyridine (5.12a)



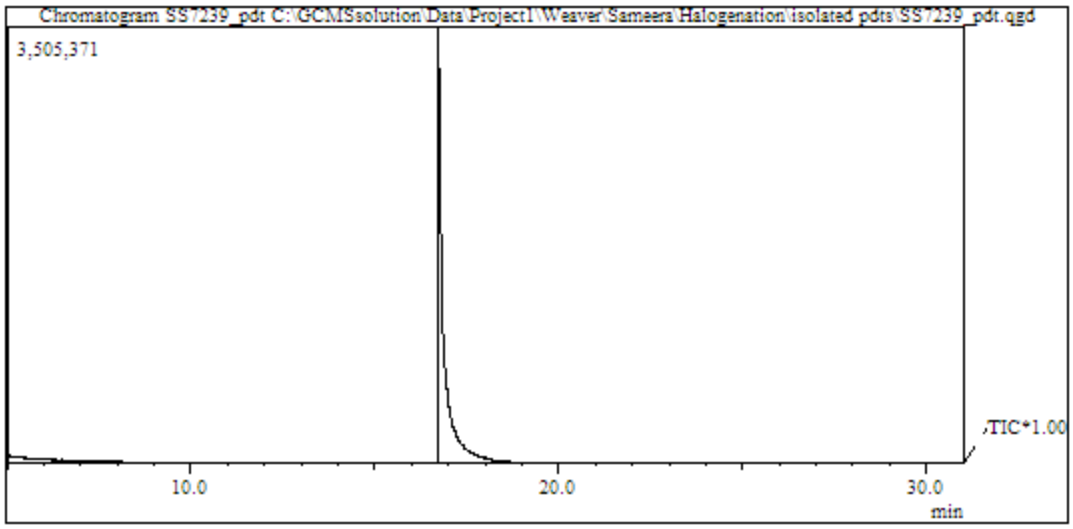
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4-(4-(*tert*-butyl)phenyl)-2,3,5,6-tetrafluoropyridine (5.12a)

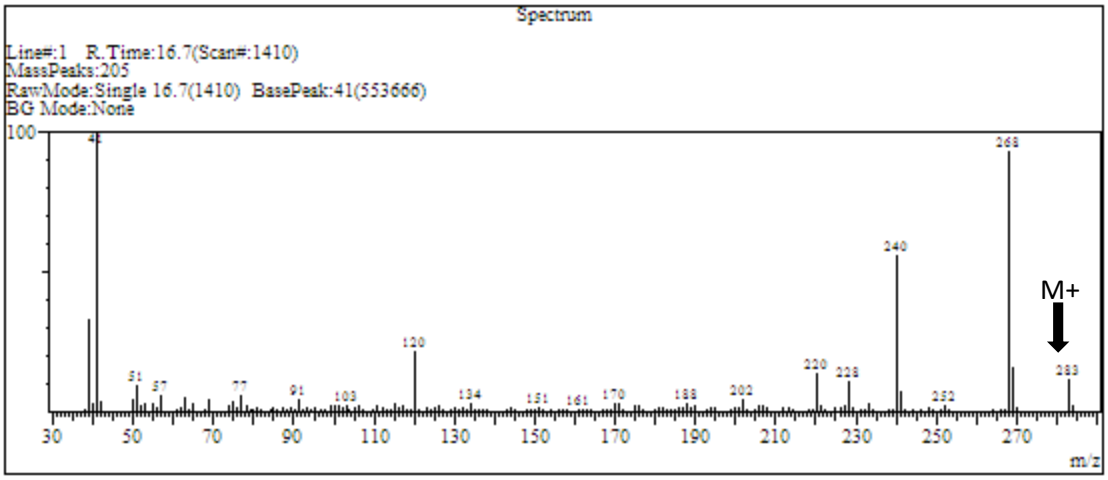


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 4-(4-(*tert*-butyl)phenyl)-2,3,5,6-tetrafluoropyridine (5.12a)

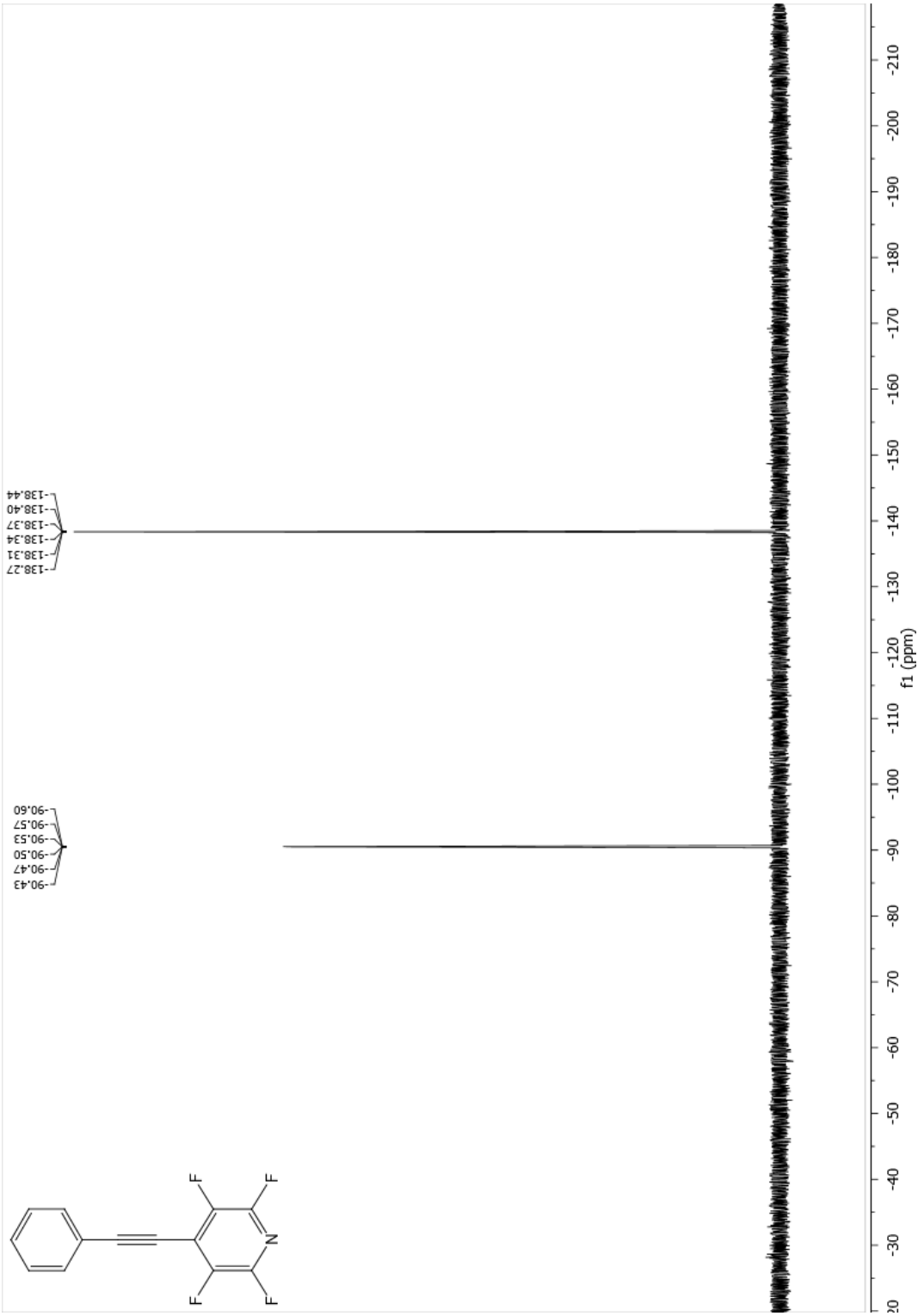


GC and MS of GC and MS of 4-(4-(*tert*-butyl)phenyl)-2,3,5,6-tetrafluoropyridine (5.12a)

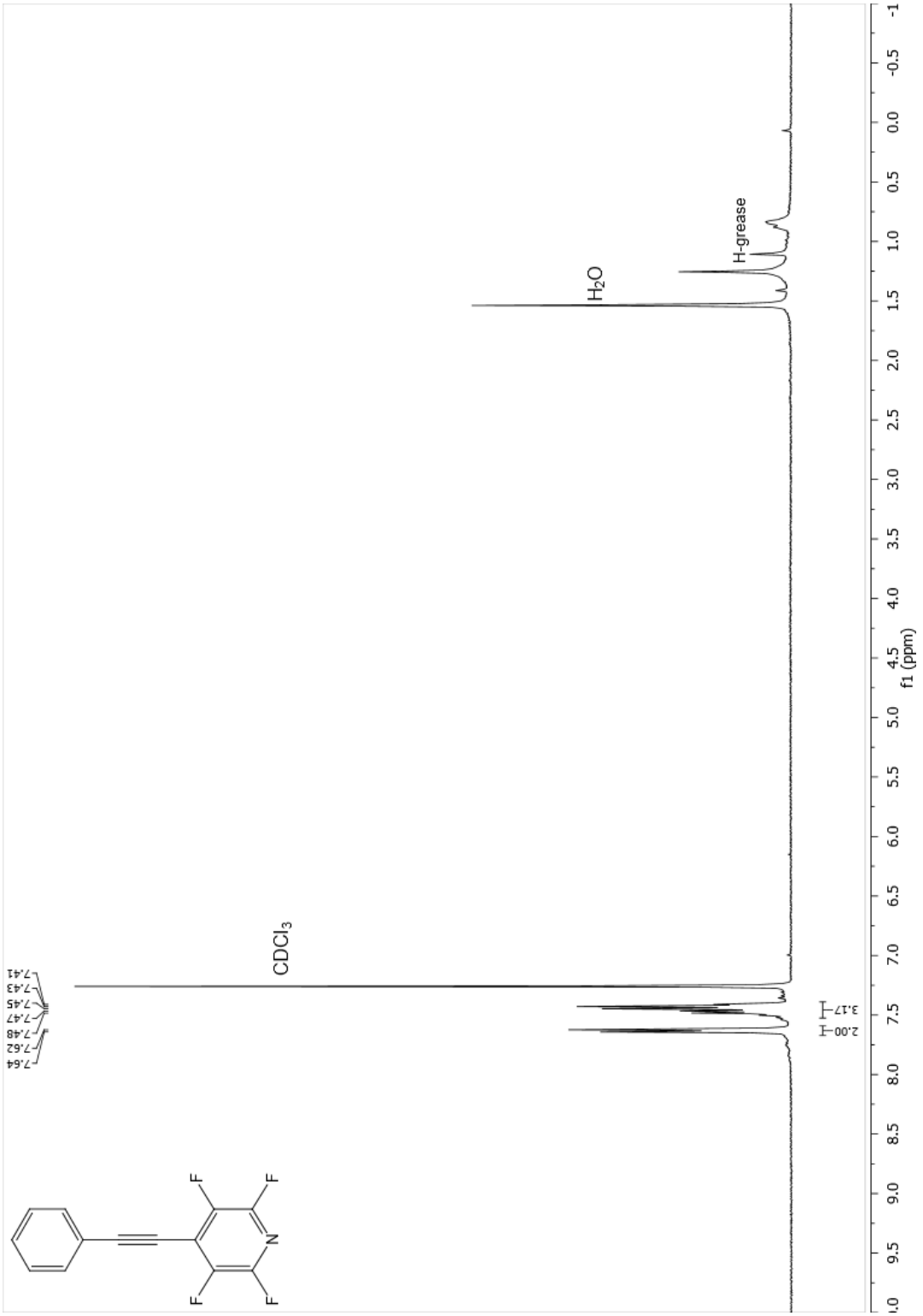




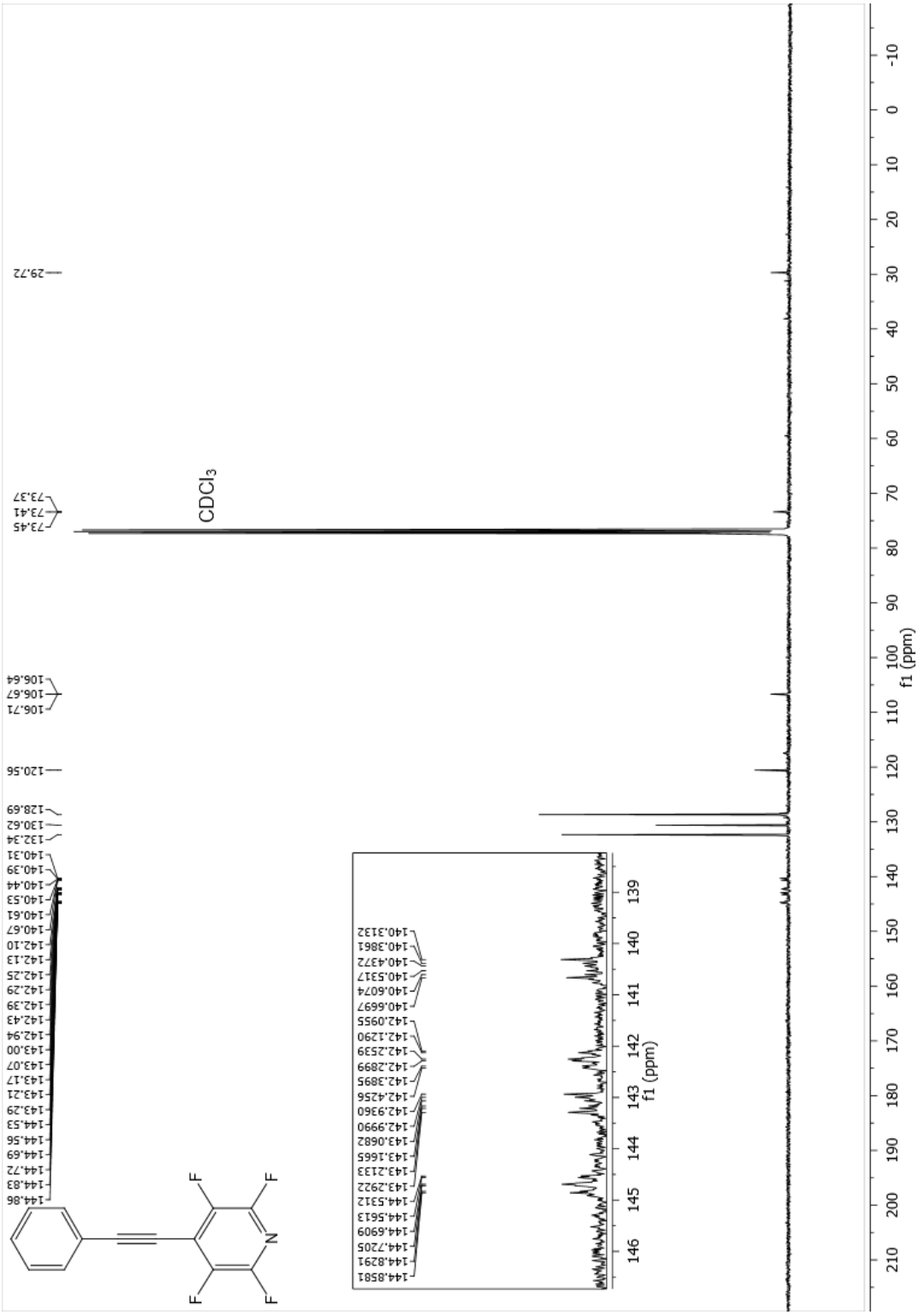
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2,3,5,6-tetrafluoro-4-(phenylethynyl)pyridine (5.12b)



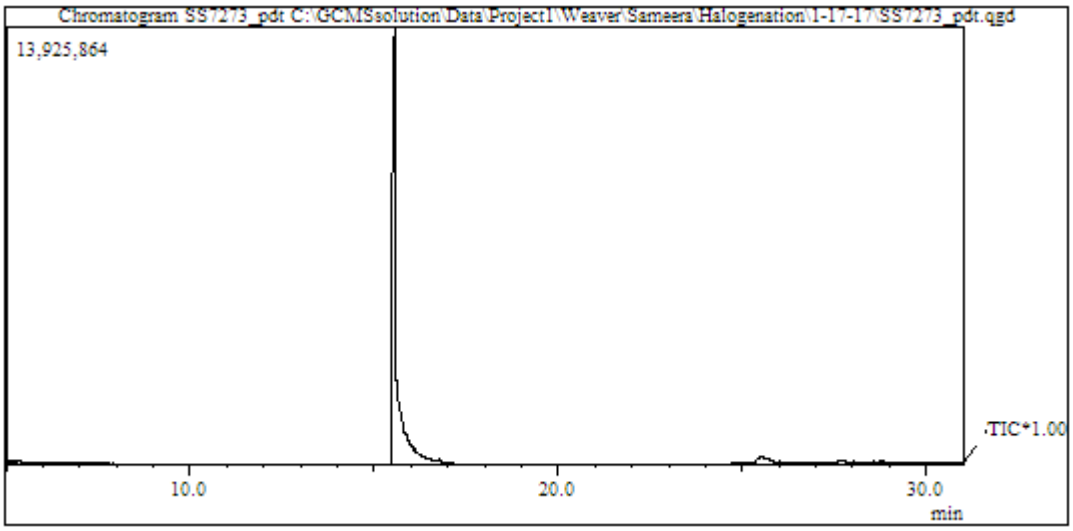
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2,3,5,6-tetrafluoro-4-(phenylethynyl)pyridine (5.12b)

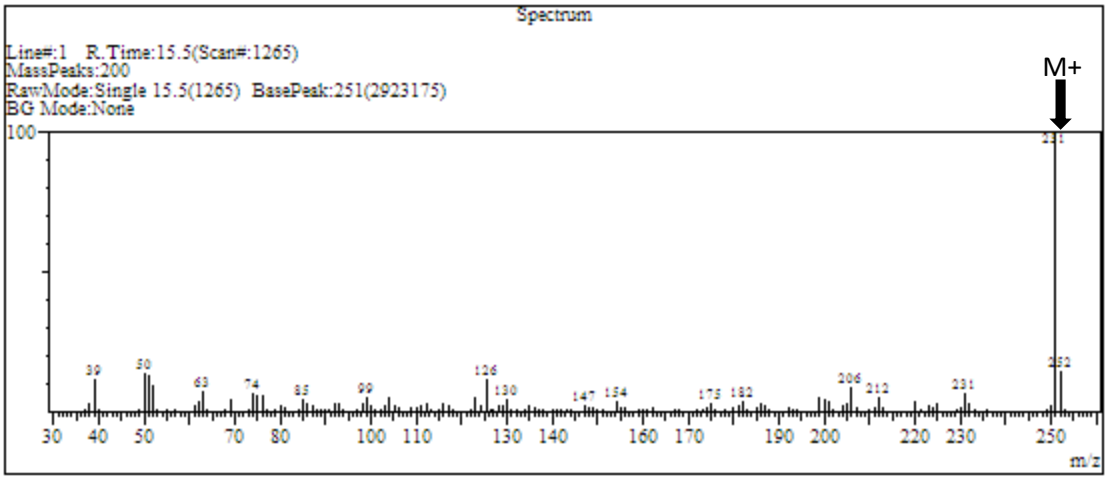


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of 2,3,5,6-tetrafluoro-4-(phenylethynyl)pyridine (5.12b)

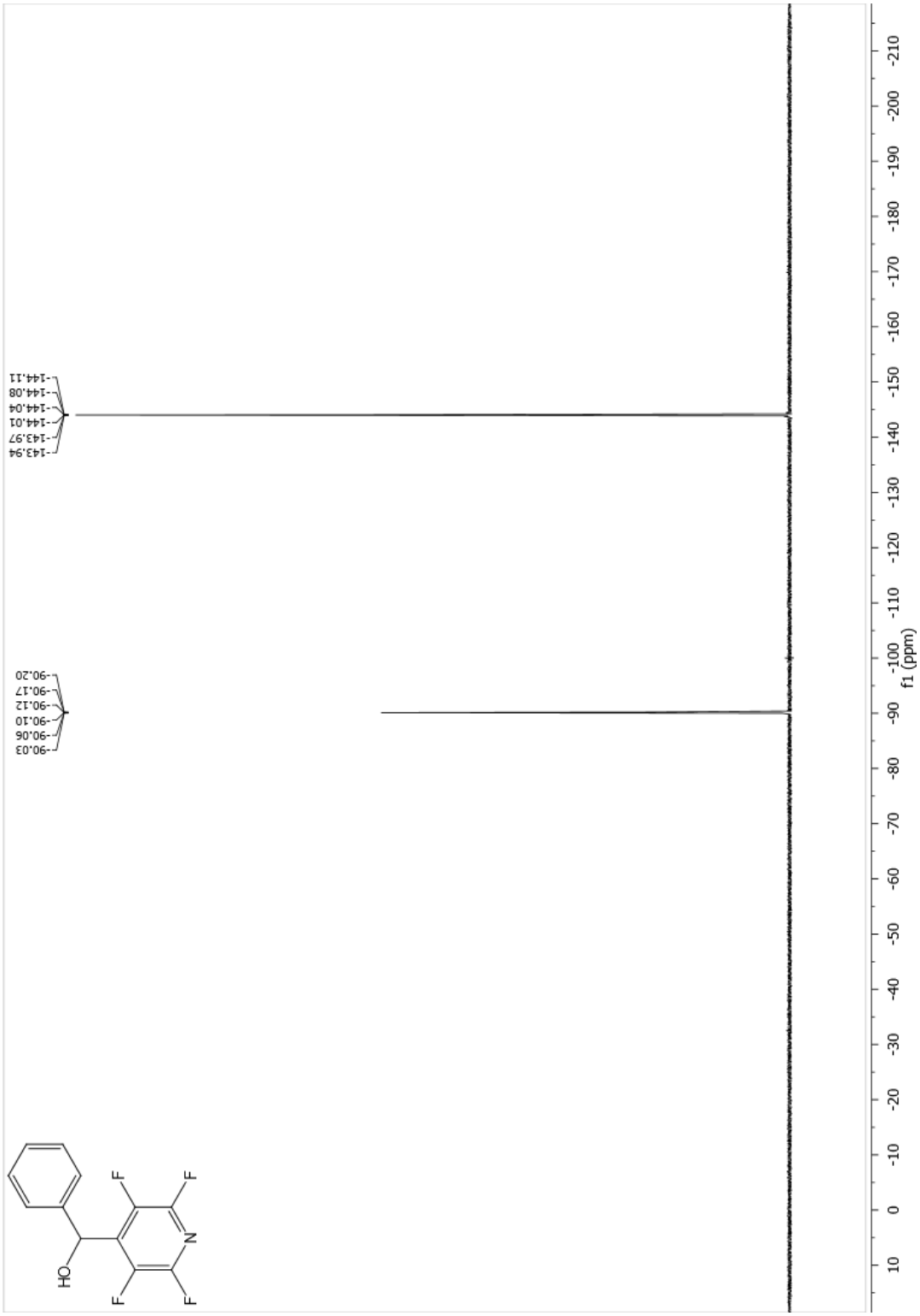


GC and MS of GC and MS of 2,3,5,6-tetrafluoro-4-(phenylethynyl)pyridine (5.12b)

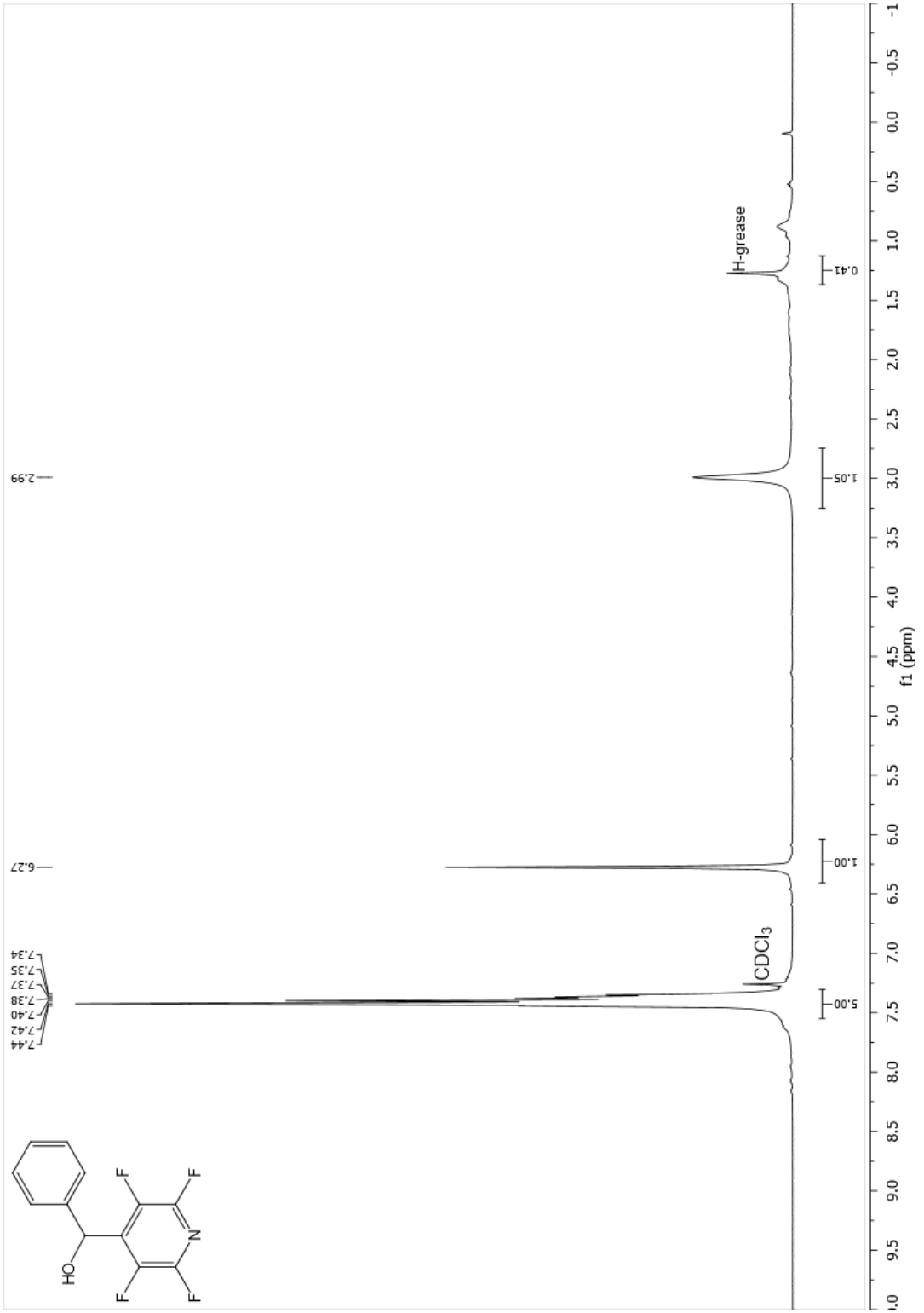




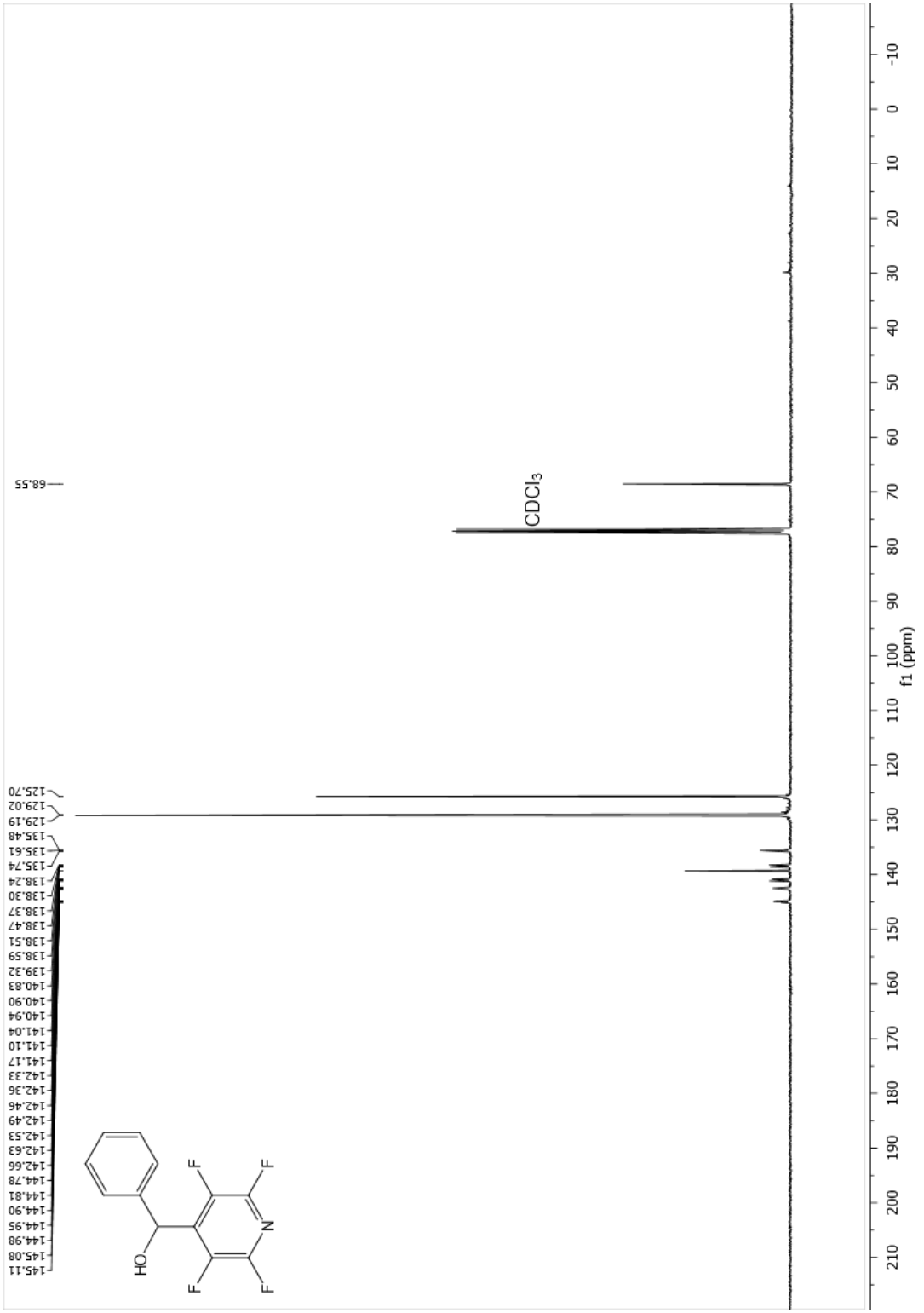
^{19}F NMR (376 MHz, $CDCl_3$, at rt) spectrum of (perfluoropyridin-4-yl)(phenyl)methanol (5.12c)



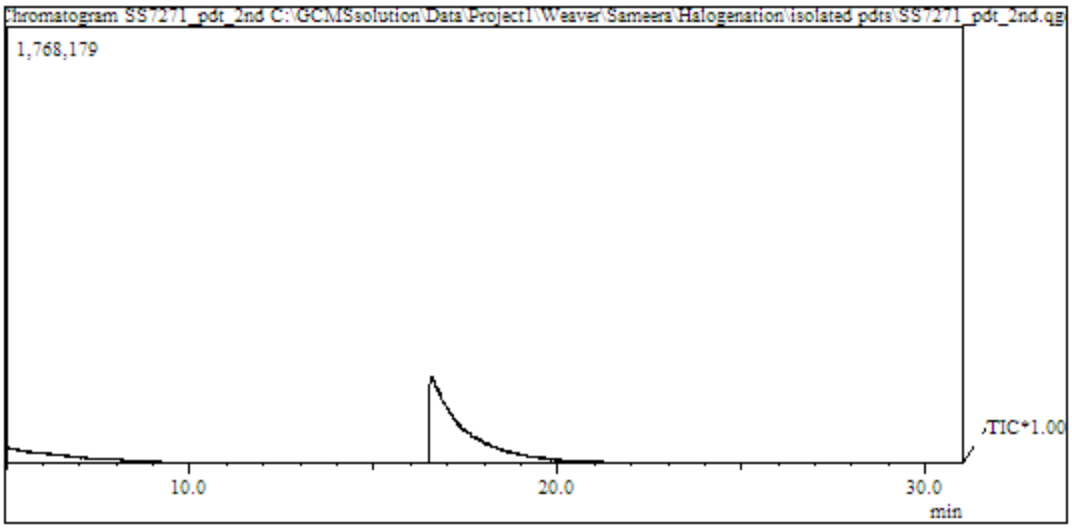
^{1}H NMR (376 MHz, $CDCl_3$, at rt) spectrum of (perfluoropyridin-4-yl)(phenyl)methanol (5.12c)

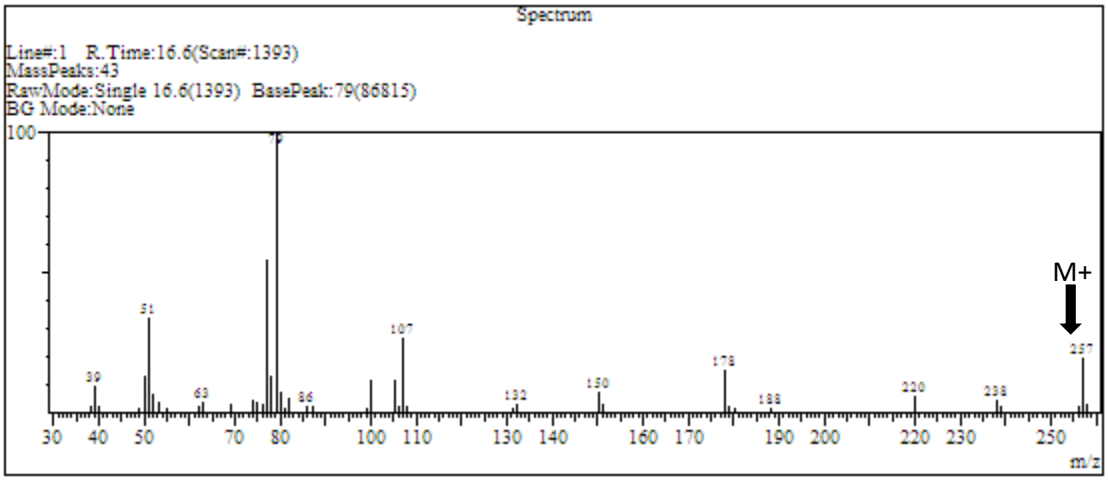


^{13}C NMR (376 MHz, $CDCl_3$, at rt) spectrum of (perfluoropyridin-4-yl)(phenyl)methanol (5.12c)



GC and MS of GC and MS of (perfluoropyridin-4-yl)(phenyl)methanol (5.12c)





REFERENCES

1. (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H., *Chem. Rev.* **2014**, *114*, 2432-2506; (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V., *Chem. Soc. Rev.* **2008**, *37*, 320-330; (c) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M., *ChemBioChem.* **2004**, *5*, 637-643.
2. (a) Selby, T. P.; Bereznak, J. F.; Bisaha, J. J.; Ding, A. X.; Gopalsamuthiram, V.; Hanagan, M. A.; Long, J. K.; Taggi, A. E., Fungicidal substituted azoles. WO 2009137651 A8: **2010**; (b) Gregory, V.; Taggi, A. E., Fungicidal mixtures. WO 2011056463 A2: **2011**.
3. Hird, M., *Chem. Soc. Rev.* **2007**, *36*, 2070-2095.
4. Tsuzuki, T.; Shirasawa, N.; Suzuki, T.; Tokito, S., *Adv. Mater.* **2003**, *15*, 1455-1458.
5. Kitamura, T.; Wada, Y.; Yanagida, S., *J. Fluorine Chem.* **2000**, *105*, 305-311.
6. (a) Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Tokito, S.; Taga, Y., *J. Am. Chem. Soc.* **2000**, *122*, 1832-1833; (b) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R., *Chem. Commun.* **2007**, 1003-1022.
7. Harper, D. B.; O'Hagan, D., *Nat. Prod. Rep.* **1994**, *11*, 123-133.
8. O'Hagan, D.; B. Harper, D., *J. Fluorine Chem.* **1999**, *100*, 127-133.
9. (a) Amii, H.; Uneyama, K., *Chem. Rev.* **2009**, *109*, 2119-2183; (b) Fujiwara, T.; O'Hagan, D., *J. Fluorine Chem.* **2014**, *167*, 16-29.
10. Pauling, L., *J. Am. Chem. Soc.* **1932**, *54*, 3570-3582.
11. Furuya, T.; Kamlet, A. S.; Ritter, T., *Nature* **2011**, *473*, 470-477.
12. Furuya, T.; Strom, A. E.; Ritter, T., *J. Am. Chem. Soc.* **2009**, *131*, 1662-1663.
13. Lee, H. G.; Milner, P. J.; Buchwald, S. L., *Org. Lett.* **2013**, *15*, 5602-5605.
14. Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q., *Angew. Chem. Int. Ed.* **2011**, *50*, 9081-9084.
15. Banks, R. E., Smart, B.E., Tatlow, J.C, *Organofluorine Chemistry Principles and Commercial Applications*. Plenum: New York, **1994**.
16. (a) Senaweera, S. M.; Singh, A.; Weaver, J. D., *J. Am. Chem. Soc.* **2014**, *136*, 3002-3005; (b) Kuehnel, M. F.; Lentz, D.; Braun, T., *Angew. Chem. Int. Ed.* **2013**, *52*, 3328-3348.
17. (a) Arndt, P.; Spannenberg, A.; Baumann, W.; Burlakov, V. V.; Rosenthal, U.; Becke, S.; Weiss, T., *Organometallics* **2004**, *23*, 4792-4795; (b) Edelbach, B. L.; Fazlur Rahman, A. K.; Lachicotte, R. J.; Jones, W. D., *Organometallics* **1999**, *18*, 3170-3177.

18. (a) Aizenberg, M.; Milstein, D., *J. Am. Chem. Soc.* **1995**, *117*, 8674-8675; (b) Aizenberg, M.; Milstein, D., *Science* **1994**, *265*, 359-361.
19. (a) Archibald, S. J.; Braun, T.; Gaunt, J. A.; Hobson, J. E.; Perutz, R. N., *J. Chem. Soc., Dalton Trans.* **2000**, 2013-2018; (b) Fischer, P.; Götz, K.; Eichhorn, A.; Radius, U., *Organometallics* **2012**, *31*, 1374-1383.
20. Breyer, D.; Braun, T.; Kläring, P., *Organometallics* **2012**, *31*, 1417-1424.
21. Zhan, J.-H.; Lv, H.; Yu, Y.; Zhang, J.-L., *Adv. Synth. Catal.* **2012**, *354*, 1529-1541.
22. Jones, R. G.; Gilman, H., *Chem. Rev.* **1954**, *54*, 835-890.
23. Blanksby, S. J.; Ellison, G. B., *Acc. Chem. Res.* **2003**, *36*, 255-263.
24. (a) Den, T. S.; Frey, H.-M.; Leutwyler, S., *J. Chem. Phys.* **2014**, *141*, 194303; (b) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E., *Chem. Rev.* **1994**, *94*, 373-431.
25. Makishima, A.; Tanaka, R.; Nakamura, E., *Anal. Sci.* **2009**, *25*, 1181-1187.
26. Bosque, R.; Clot, E.; Fantacci, S.; Maseras, F.; Eisenstein, O.; Perutz, R. N.; Renkema, K. B.; Caulton, K. G., *J. Am. Chem. Soc.* **1998**, *120*, 12634-12640.
27. Arora, A.; Weaver, J. D., *Acc. Chem. Res.* **2016**, *49*, 2273-2283.
28. Kariv-Miller, E.; Vajtner, Z., *J. Org. Chem.* **1985**, *50*, 1394-1399.
29. Konovalov, V. V.; Laev, S. S.; Beregovaya, I. V.; Shchegoleva, L. N.; Shteingarts, V. D.; Tsvetkov, Y. D.; Bilkis, I., *J. Phys. Chem. A* **2000**, *104*, 352-361.
30. Shchegoleva, L. N.; Beregovaya, I. V.; Schastnev, P. V., *Chem. Phys. Lett.* **1999**, *312*, 325-332.
31. (a) Shteingarts, V. D., *J. Fluorine Chem.* **2007**, *128*, 797-805; (b) Laev, S. S.; Shteingarts, V. D.; Bilkis, I. I., *Tetrahedron Lett.* **1995**, *36*, 4655-4658.
32. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C., *Chem. Rev.* **2013**, *113*, 5322-5363.
33. Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P., *J. Am. Chem. Soc.* **2008**, *130*, 12886-12887.
34. Nicewicz, D. A.; MacMillan, D. W. C., *Science* **2008**, *322*, 77-80.
35. Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J., *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.
36. (a) Weaver, J. D., *Synlett* **2014**, *25*, 1946-1952; (b) Singh, A.; Kubik, J. J.; Weaver, J. D., *Chem. Sci.* **2015**, *6*, 7206-7212; (c) Singh, K.; Staig, S. J.; Weaver, J. D., *J. Am. Chem. Soc.* **2014**, *136*, 5275-5278; (d) Singh, A.; Fennell, C. J.; Weaver, J. D., *Chem. Sci.* **2016**.
37. Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J., *Nat Chem* **2012**, *4*, 854-859.
38. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C., *Chem. Rev.* **2013**, *113*, 5322-5363.
39. (a) Narayanam, J. M. R.; Stephenson, C. R. J., *Chem. Soc. Rev.* **2011**, *40*, 102-113; (b) Corrigan, N.; Shanmugam, S.; Xu, J.; Boyer, C., *Chem. Soc. Rev.* **2016**, *45*, 6165-6212; (c) Zeitler, K., *Angewandte Chemie-International Edition* **2009**, *48*, 9785-9789; (d) Xuan, J.; Xiao, W.-J., *Angew. Chem. Int. Ed.* **2012**, *51*, 6828-6838.
40. Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F., Photochemistry and Photophysics of Coordination Compounds: Iridium. *Photochemistry and Photophysics of Coordination Compounds II*, Balzani, V.; Campagna, S., Eds. Springer Berlin Heidelberg: Berlin, Heidelberg, **2007**; pp 143-203.
41. Beletskaya, I. P.; Artamkina, G. A.; Mil'chenko, A. Y.; Sazonov, P. K.; Shtern, M. M., *J. Phys. Org. Chem.* **1996**, *9*, 319-328.
42. (a) http://www.chem.wisc.edu/areas/reich/pkatable/. (accessed 6.8.2017); (b) Bordwell, F. G., *Acc. Chem. Res.* **1988**, *21*, 456-463; (c) http://ccc.chem.pitt.edu/wipf/MechOMs/evans_pKa_table.pdf. (accessed 6.8.2017).

43. Lu, J.; Khetrapal, N. S.; Johnson, J. A.; Zeng, X. C.; Zhang, J., *J. Am. Chem. Soc.* **2016**, *138*, 15805-15808.
44. Schmidbauer, S.; Hohenleutner, A.; König, B., *Beilstein Journal of Organic Chemistry* **2013**, *9*, 2088-2096.
45. (a) K. Morita, D.; A. David, S.; Tumas, W.; K. Morita, D.; R. Pesiri, D.; H. Glaze, W., *Chem. Commun.* **1998**, 1397-1398; (b) Hirai, T.; Hamasaki, A.; Nakamura, A.; Tokunaga, M., *Org. Lett.* **2009**, *11*, 5510-5513.
46. Zhang, J.; Chen, W.; Rojas, A. J.; Jucov, E. V.; Timofeeva, T. V.; Parker, T. C.; Barlow, S.; Marder, S. R., *J. Am. Chem. Soc.* **2013**, *135*, 16376-16379.
47. (a) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J., *Org. Lett.* **2011**, *13*, 276-279; (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q., *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; (c) Lafrance, M.; Shore, D.; Fagnou, K., *Org. Lett.* **2006**, *8*, 5097-5100; (d) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M., *Org. Lett.* **2009**, *11*, 3346-3349; (e) Wei, Y.; Su, W., *J. Am. Chem. Soc.* **2010**, *132*, 16377-16379.
48. A small amount ~7% of hydrodebromination product was observed and was seperated from the intended product. This was observed previously: Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem*. 2012, 4, 854. A small amount ~7% of hydrodebromination product was observed and was seperated from the intended product. This was observed previously: Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem*. **2012**, 4, 854.
49. Selivanova, G. A.; Reshetov, A. V.; Beregovaya, I. V.; Vasil'eva, N. V.; Bagryanskaya, I. Y.; Shteingarts, V. D., *J. Fluorine Chem.* **2012**, *137*, 64-72.
50. Reißmann, M.; Schäfer, A.; Jung, S.; Müller, T., *Organometallics* **2013**, *32*, 6736-6744.
51. Jäger-Fiedler, U.; Klahn, M.; Arndt, P.; Baumann, W.; Spannenberg, A.; Burlakov, V. V.; Rosenthal, U., *J. Mol. Catal. A: Chem.* **2007**, *261*, 184-189.
52. Lv, H.; Cai, Y.-B.; Zhang, J.-L., *Angew. Chem. Int. Ed.* **2013**, *52*, 3203-3207.
53. Andrews, R. S.; Becker, J. J.; Gagné, M. R., *Angew. Chem. Int. Ed.* **2012**, *51*, 4140-4143.
54. (a) Knochel, P.; Molander, G. A., *Comprehensive Organic Synthesis*. Elsevier Science: **2014**; (b) Ravelli, D.; Protti, S.; Fagnoni, M., *Chem. Rev.* **2016**, *116*, 9850-9913.
55. Singh, A.; Kubik, J. J.; Weaver, J. D., *Chemical Science* **2015**, *6*, 7206-7212.
56. (a) Degirmenci, I.; Coote, M. L., *The Journal of Physical Chemistry A* **2016**, *120*, 1750-1755; (b) Lalevée, J.; Allonas, X.; Fouassier, J.-P., *J. Org. Chem.* **2005**, *70*, 814-819.
57. Meyer, A. U.; Slanina, T.; Yao, C.-J.; König, B., *ACS Catalysis* **2016**, *6*, 369-375.
58. Crich, D.; Hwang, J.-T., *J. Org. Chem.* **1998**, *63*, 2765-2770.
59. (a) Miyaura, N.; Suzuki, A., *Chem. Rev.* **1995**, *95*, 2457-2483; (b) Buchwald, S. L.; Fugami, K.; Hiyama, T.; Kosugi, M.; Miura, M.; Miyaura, N.; Muci, A.; Nomura, M.; Shirakawa, E.; Tamao, K., *Cross-coupling reactions: a practical guide*. Springer: **2003**; Vol. 219.
60. (a) Kinzel, T.; Zhang, Y.; Buchwald, S. L., *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075; (b) Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T., *Org. Lett.* **2005**, *7*, 4915-4917; (c) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F., *J. Fluorine Chem.* **2002**, *117*, 115-120; (d) Coe, P. L.; Pearl, G. M., *J. Organomet. Chem.* **1971**, *31*, 55-57.
61. Miyaura, N.; Yanagi, T.; Suzuki, A., *Synth. Commun.* **1981**, *11*, 513-519.
62. Lennox, A. J. J.; Lloyd-Jones, G. C., *Chem. Soc. Rev.* **2014**, *43*, 412-443.
63. (a) Izmer, V. V.; Lebedev, A. Y.; Nikulin, M. V.; Ryabov, A. N.; Asachenko, A. F.; Lygin, A. V.; Sorokin, D. A.; Voskoboynikov, A. Z., *Organometallics* **2006**, *25*, 1217-1229; (b) Leoni, L.; Puttreddy, R.; Jurček, O.; Mele, A.; Giannicchi, I.; Mihan, F. Y.; Rissanen, K.; Dalla Cort, A., *Chemistry – A European Journal* **2016**, *22*, 18714-18717; (c) Hofer, M.; Genoux, A.; Kumar, R.; Nevado, C., *Angew. Chem. Int. Ed.* **2017**, *56*, 1021-1025.

64. Lindner, S.; Bräse, S.; Masters, K.-S., *J. Fluorine Chem.* **2015**, *179*, 102-105.
65. (a) Ghorbani-Vaghei, R.; Shahbazi, H.; Veisi, H., *Tetrahedron Lett.* **2012**, *53*, 2325-2327; (b) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A., *J. Am. Chem. Soc.* **2004**, *126*, 15770-15776.
66. Burton, D. J.; Jairaj, V., *J. Fluorine Chem.* **2004**, *125*, 673-680.
67. (a) Sun, A. D.; Love, J. A., *Org. Lett.* **2011**, *13*, 2750-2753; (b) Yoshikai, N.; Mashima, H.; Nakamura, E., *J. Am. Chem. Soc.* **2005**, *127*, 17978-17979; (c) Nakamura, Y.; Yoshikai, N.; Ilies, L.; Nakamura, E., *Org. Lett.* **2012**, *14*, 3316-3319; (d) Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S., *Organometallics* **2014**, *33*, 3669-3672.
68. Singh, A.; Teegardin, K.; Kelly, M.; Prasad, K. S.; Krishnan, S.; Weaver, J. D., *J. Organomet. Chem.* **2015**, *776*, 51-59.
69. Arora, A.; Teegardin, K. A.; Weaver, J. D., *Org. Lett.* **2015**, *17*, 3722-3725.
70. Furukawa, T.; Tobisu, M.; Chatani, N., *J. Am. Chem. Soc.* **2015**, *137*, 12211-12214.
71. Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M., *Tetrahedron* **1971**, *27*, 3575-3579.
72. Li, J. J., Minisci reaction. *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, Springer Berlin Heidelberg: Berlin, Heidelberg, **2009**; pp 361-362.
73. Minisci, F.; Vismara, E.; Fontana, F., *Heterocycles* **1989**, *28*, 489-519.
74. Bunnett, J. F., *Quarterly Reviews, Chemical Society* **1958**, *12*, 1-16.
75. Rossi, R. A., *Acc. Chem. Res.* **1982**, *15*, 164-170.
76. Senaweera, S. M.; Weaver, J. D., *J. Org. Chem.* **2014**, *79*, 10466-10476.
77. Senaweera, S.; Weaver, J. D., *J. Org. Chem.* **2014**, *79*, 10466-10476.
78. (a) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T., *Chem. Rev.* **2015**, *115*, 931-972; (b) Kiplinger, J. L.; Richmond, T. G., *Chem. Commun.* **1996**, 1115-1116; (c) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E., *Chem. Rev.* **1994**, *94*, 373-431; (d) Amii, H.; Uneyama, K., *Chem. Rev.* **2009**, *109*, 2119-2183.
79. Ritter, S. K. Dual C–F/C–H functionalization unveiled. http://cen.acs.org/articles/94/i10/Dual-CFCH-functionalization-unveiled.html (accessed 6.5.2017).
80. http://www.sigmaaldrich.com/catalog/product/aldrich/158798?lang=en&region=US. (accessed 6.23.2017).
81. http://www.sigmaaldrich.com/catalog/product/aldrich/316679?lang=en&region=US. (accessed 6.23.2017).
82. Roe, A., Preparation of Aromatic Fluorine Compounds from Diazonium Fluoborates. *Organic Reactions*, John Wiley & Sons, Inc.: **2004**.
83. Finger, G. C.; Kruse, C. W., *J. Am. Chem. Soc.* **1956**, *78*, 6034-6037.
84. Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A., *J. Org. Chem.* **1979**, *44*, 3872-3881.
85. Fier, P. S.; Hartwig, J. F., *J. Am. Chem. Soc.* **2012**, *134*, 10795-10798.
86. Burdeniuc, J.; Jedicka, B.; Crabtree, R. H., *Chem. Ber.* **1997**, *130*, 145-154.
87. Anslyn, E. V.; Dougherty, D. A., *Modern Physical Organic Chemistry*. University Science Books: Sausalito, CA, **2006**.
88. Meldrum, A. N., *J. Chem. Soc., Trans.* **1908**, *93*, 598-601.
89. Davidson, D.; Bernhard, S. A., *J. Am. Chem. Soc.* **1948**, *70*, 3426-3428.
90. Nakamura, S.; Hirao, H.; Ohwada, T., *J. Org. Chem.* **2004**, *69*, 4309-4316.
91. Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A., *J. Am. Chem. Soc.* **1984**, *106*, 6759-6767.
92. Hrubowchak, D. M.; Smith, F. X., *Tetrahedron Lett.* **1983**, *24*, 4951-4954.

93. Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A., *Tetrahedron* **1997**, *53*, 12867-12874.
94. Dhuru, S.; Mohe, N.; Salunkhe, M., *Synth. Commun.* **2001**, *31*, 3653.
95. Chan, C.-C.; Huang, X. I. A. N., *Synthesis* **1984**, *1984*, 224-225.
96. (a) Mehta, B. P.; Shah, R.; Shrikhande, A. A.; Mamidanna, V. A process for the preparation of [2-(2,6-dichloro anilino) phenyl] acetoxy acetic acid. PCT/IN2004/000049, **2005**; (b) Franklin, R.; Tyson, R. G.; Golding, B. T.; Whomsley, R. Prodrugs of guanfacine. PCT/GB2010/051544, **2011**; (c) Guo, J.; Chen, X.-F.; Liu, J.; Lin, H.-Y.; Han, H.-W.; Liu, H.-C.; Huang, S.-C.; Shahla, B. K.; Kulek, A.; Qi, J.-L.; Wang, X.-M.; Ling, L.-J.; Yang, Y.-H., *Chemical Biology & Drug Design* **2014**, *84*, 603-615.
97. Chen, Z.; Jin, Y.; Stang, P. J., *J. Org. Chem.* **1987**, *52*, 4115-4117.
98. Pinhey, J. T.; Rowe, B. A., *Tetrahedron Lett.* **1980**, *21*, 965-968.
99. Chambers, R. D., *Fluorine in Organic Chemistry*. CRC Press LLC: New York, **2004**; Vol. 57.
100. (a) Kimmel, K. L.; Weaver, J. D.; Ellman, J. A., *Chem. Sci.* **2012**, *3*, 121-125; (b) Ivanov, A. S., *Chem. Soc. Rev.* **2008**, *37*, 789-811.
101. Sato, M.; Ban, H.; Kaneko, C., *Tetrahedron Lett.* **1997**, *38*, 6689-6692.
102. Our tentative assignment of the *N*-arylated product is one in which the amine has undergone arylation and dealkylation. The *N*-substitution occurs at the same site as the MA addition. Our tentative assignment of the N-arylated product is one in which the amine has undergone arylation and dealkylation. The N-substitution occurs at the same site as the MA addition.
103. Olmstead, W. N.; Bordwell, F. G., *J. Org. Chem.* **1980**, *45*, 3299-3305.
104. (a) Leibfarth, F. A.; Wolffs, M.; Campos, L. M.; Delany, K.; Treat, N.; Kade, M. J.; Moon, B.; Hawker, C. J., *Chem. Sci.* **2012**, *3*, 766-771; (b) Collins, K. D.; Oliveira, J. M.; Guazzelli, G.; Sautier, B.; De Grazia, S.; Matsubara, H.; Helliwell, M.; Procter, D. J., *Chem. Eur. J.* **2010**, *16*, 10240-10249.
105. Fillion, E.; Dumas, A. M., *J. Org. Chem.* **2008**, *73*, 2920-2923.
106. McNab, H., *Chem. Soc. Rev.* **1978**, *7*, 345-358.
107. Bélanger, G.; Lévesque, F.; Pâquet, J.; Barbe, G., *J. Org. Chem.* **2005**, *70*, 291-296.
108. Nahm, S.; Weinreb, S. M., *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
109. http://aspirasci.com/faye-blocks?orderby=10. (accessed 6.7.2017).
110. http://www.sigmaaldrich.com/technical-documents/articles/chemistry/professor-and-product-portal/jimmie-weaver.html. (accessed 6.7.2017).
111. Teegardin, K. A.; Weaver, J. D., *Chem. Commun.* **2017**, *53*, 4771-4774.
112. Day, J. I.; Weaver, J. D., *J. Org. Chem.* **2017**.
113. Flowers, W. T.; Haszeldine, R. N.; Majid, S. A., *Tetrahedron Lett.* **1967**, *8*, 2503-2505.
114. Yakobson, G. G.; Knunyants, I. L., *Syntheses of fluoroorganic compounds*. Springer-Verlag, Berlin: New York, **1985**.
115. Liang, T.; Neumann, C. N.; Ritter, T., *Angew. Chem. Int. Ed.* **2013**, *52*, 8214-8264.
116. Froese, R. D. J.; Whiteker, G. T.; Peterson, T. H.; Arriola, D. J.; Renga, J. M.; Shearer, J. W., *J. Org. Chem.* **2016**, *81*, 10672-10682.
117. Banks, R. E.; Haszeldine, R. N.; Latham, J. V.; Young, I. M., *J. Chem. Soc. (Resumed)* **1965**, 594-597.

118. (a) Otsuka, M.; Endo, K.; Shibata, T., *Chem. Commun.* **2010**, *46*, 336-338; (b) Schimler, S. D.; Ryan, S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S., *J. Org. Chem.* **2015**, *80*, 12137-12145.

119. (a) Artamkina, G. A.; Egorov, M. P.; Beletskaya, I. P., *Chem. Rev.* **1982**, *82*, 427-459; (b) Terrier, F., *Chem. Rev.* **1982**, *82*, 77-152.
120. (a) Semmelhack, M. F.; Chlenov, A.; Ho, D. M., *J. Am. Chem. Soc.* **2005**, *127*, 7759-7773; (b) Houghton, R. P.; Voyle, M.; Price, R., *J. Chem. Soc., Perkin Trans. 1* **1984**, 925-931; (c) Bräse, S., *Tetrahedron Lett.* **1999**, *40*, 6757-6759.
121. (a) Cambie, R. C.; Clark, G. R.; Coombe, S. L.; Coulson, S. A.; Rutledge, P. S.; Woodgate, P. D., *J. Organomet. Chem.* **1996**, *507*, 1-21; (b) Pearson, A. J.; Park, J. G.; Yang, S. H.; Chuang, Y.-H., *J. Chem. Soc., Chem. Commun.* **1989**, 1363-1364; (c) Kamikawa, K.; Kinoshita, S.; Furusyo, M.; Takemoto, S.; Matsuzaka, H.; Uemura, M., *J. Org. Chem.* **2007**, *72*, 3394-3402; (d) Cambie, R. C.; Janssen, S. J.; Rutledge, P. S.; Woodgate, P. D., *J. Organomet. Chem.* **1991**, *420*, 387-418; (e) Pearson, A. J.; Park, J. G.; Zhu, P. Y., *J. Org. Chem.* **1992**, *57*, 3583-3589; (f) Pearson, A. J.; Shin, H., *J. Org. Chem.* **1994**, *59*, 2314-2323.
122. Janetka, J. W.; Rich, D. H., *J. Am. Chem. Soc.* **1997**, *119*, 6488-6495.
123. Houghton, R. P.; Voyle, M.; Price, R., *J. Organomet. Chem.* **1983**, *259*, 183-188.
124. Walton, J. W.; Williams, J. M. J., *Chem. Commun.* **2015**, *51*, 2786-2789.
125. Shimizu, K.; Costa Gomes, M. F.; Pádua, A. A. H.; Rebelo, L. P. N.; Canongia Lopes, J. N., *J. Phys. Chem. B.* **2009**, *113*, 9894-9900.
126. Pace, C. J.; Gao, J., *Acc. Chem. Res.* **2013**, *46*, 907-915.
127. Vaganova, T. A.; Kusov, S. Z.; Rodionov, V. I.; Shundrina, I. K.; Malykhin, E. V., *Russ. Chem. Bull.* **2007**, *56*, 2239-2246.
128. (a) http://www.sigmaaldrich.com/catalog/product/aldrich/t22209?lang=en&region=US&gclid=EAIaIQobChMI3c7i7ZHr1AIVyrbACh1DGQSDEAAYASAAEgJe0PD_BwE. (accessed 7.2.2017); (b) http://www.sigmaaldrich.com/catalog/product/aldrich/158402?lang=en&region=US&gclid=CIzOp5uS69QCFUm5wAodBKMEVg (accessed 7.2.2017).
129. Cioslowski, J.; Liu, G.; Moncrieff, D., *J. Phys. Chem. A.* **1997**, *101*, 957-960.
130. Shipilov, A. I.; Zolotkova, E. E.; Igumnov, S. M., *Russ. J. Org. Chem.* **2004**, *40*, 1117-1120.
131. (a) Burwell, R. L.; Pearson, R. G., *J. Phys. Chem.* **1966**, *70*, 300-302; (b) Tolman, R. C., *Proc. Natl. Acad. Sci. U.S.A.* **1925**, *11*, 436-439.
132. Luo, Y. R., *Comprehensive Handbook of Chemical Bond Energies*. CRC Press,: Boca Raton, Florida, **2007**.
133. (a) Liotta, C. L.; Harris, H. P., *J. Am. Chem. Soc.* **1974**, *96*, 2250-2252; (b) Steed, J. W.; Atwood, J. L., *Supramol. Chem.* John Wiley & Sons, Ltd.: United Kingdom, **2009**.
134. Hammond, G. S., *J. Am. Chem. Soc.* **1955**, *77*, 334-338.
135. (a) Althagbi, H. I.; Edwards, A. J.; Nicholson, B. K.; Reason, D. A.; Saunders, G. C.; Sim, S. A.; van der Heijden, D. A., *Cryst. Growth Des.* **2016**, *16*, 174-188; (b) Wheeler, S. E., *Acc. Chem. Res.* **2013**, *46*, 1029-1038.
136. Giese, M.; Albrecht, M.; Rissanen, K., *Chem. Rev.* **2015**, *115*, 8867-8895.
137. Lv, H.; Zhan, J.-H.; Cai, Y.-B.; Yu, Y.; Wang, B.; Zhang, J.-L., *J. Am. Chem. Soc.* **2012**, *134*, 16216-16227.
138. (a) Rebek, J.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K., *J. Am. Chem. Soc.* **1987**, *109*, 5033-5035; (b) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J., *J. Chem. Soc., Perkin Trans. 2.* **2001**, 651-669.
139. https://www.organicdivision.org/orig/organic_solvents.html. (accessed 6.19.2017).
140. Miyaura, N.; Yamada, K.; Suzuki, A., *Tetrahedron Lett.* **1979**, *20*, 3437-3440.
141. Huang, H.; Liu, H.; Jiang, H.; Chen, K., *J. Org. Chem.* **2008**, *73*, 6037-6040.

142. (a) Chernichenko, K.; Lindqvist, M.; Kótai, B.; Nieger, M.; Sorochkina, K.; Pápai, I.; Repo, T., *J. Am. Chem. Soc.* **2016**, *138*, 4860-4868; (b) Barbour, A. K.; Buxton, M. W.; Coe, P. L.; Stephens, R.; Tatlow, J. C., *J. Chem. Soc. (Resumed)* **1961**, 808-817.
143. Ahmadi, A.; Khalili, M.; Chavrogh, S.; Nahri-Niknafs, B., *Iran. J. Pharm. Res.* **2012**, *11*, 1027-1037.
144. (a) Martinez, C. R.; Iverson, B. L., *Chem. Sci.* **2012**, *3*, 2191-2201; (b) Hori, A.; Takatani, S.; Miyamoto, T. K.; Hasegawa, M., *Cryst. Eng. Comm.* **2009**, *11*, 567-569.
145. TMSCl, formed upon delivery of the chloride may accept fluoride before diffusing away, but this is not clear at this time. TMSCl, formed upon delivery of the chloride may accept fluoride before diffusing away, but this is not clear at this time.

VITA

Senaweera Arachchilage Sameera Manusanka Senaweera

Candidate for the Degree of

Doctor of Philosophy/Education

Thesis: DEVELOPMENT OF NOVEL PHOTOCATALYTIC AND NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS FOR THE FACILE ACCESS OF FUNCTIONALIZED MULTIFLUORINATED ARENES

Major Field: Chemistry

Biographical:

Education:

Completed the requirements for the Doctor of Philosophy in Organic Chemistry at Oklahoma State University, Stillwater, Oklahoma in July, 2017.

Completed the requirements for the Bachelor of Science in Chemistry at University of Kelaniya, Sri Lanka in 2010.

Professional Memberships:

American Chemical Society